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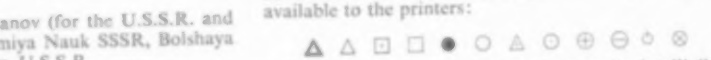

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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* 55, 661 (1933).

[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* 7, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

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g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but in^3.

New compounds should be indicated by underlining the name (for italics) at its first mention (including headings) in the experimental section only, and by giving analytical results in the form: (Found: C, 62·9; H, 5·4. $C_{18}H_{18}O_4N$ requires: C, 63·2; H 5·3%).

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ÜBER ROTE FARBSTOFFE, DIE SICH VOM 2-PHENYL-IMIDAZOLON-4(5) ABLEITEN

THEODOR WIELAND und HANS BIENER
Institut für Organische Chemie an der Johann Wolfgang Goethe-Universität
Frankfurt am Main

VOL. 15 1961

(*Received* 23 *May* 1961)

Zusammenfassung—Die aus Glycylbenzimid-hydrobromid (I) entstehenden roten Farbstoffe bilden sich über 2-Phenyl-imidazolon-4(5) (II), das als Benzylidenverbindung abgefangen werden kann. Diese Farbstoffe werden unter Anwendung der Hochspannungs-Papierelektrophorese in einem speziellen Puffer mit anderen, in der Literatur zum Teil schon beschriebenen, verglichen. Sie sind nicht mit dem Ruhemannschen Glyoxalinrot verwandt.

Abstract—Aqueous solutions of glycyl-benzoyl-imide (I) become dark red on standing for several days or on heating. The red pigments are formed via 2-phenyl-imidazolone-4(5) (II), which can be trapped by reaction with benzaldehyde. Paper electrophoresis using a special buffer system enabled comparison with other red products described in the literature or synthetized otherwise by us. None of them proved to be identical with the "glyoxaline red" of Ruhemann and Stapleton.

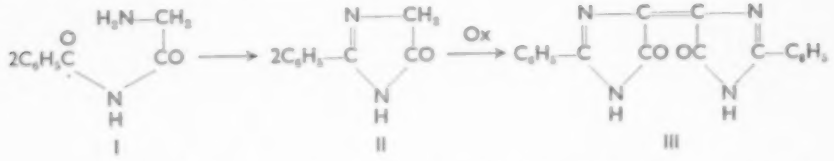
GLYCYLBENZIMID-HYDROBROMID (I), das von Wieland und Hennig[1] durch Kondensation von Azidoacetylchlorid mit Benzamid und Reduktion der Azidogruppe mit Bromwasserstoff/Eisessig erhalten wurde, ist ein farbloses, kristallines Salz, das bei längerem Aufbewahren, durch Erhitzen auf 140° oder in wässriger Lösung eine interessante Umwandlung erfährt. Es bildet sich dabei neben zahlreichen farblosen Zersetzungsprodukten wie Glycin, Glycinamid, Benzoesäure, Hippuramid in kleiner Menge ein intensiv roter Farbstoff. Er ist in Wasser, Äther, Chloroform nahezu unlöslich, besser löslich in Essigester, Alkohol, gut in Butanol (mit dem man ihn aus alkalischer Lösung ausschütteln kann) und Dimethylformamid. Während die Löslichkeit in Säuren nur schwach ausgeprägt ist, lösen Alkalien und Pyridin ausgezeichnet mit tief permanganatroter Farbe. Die Farbintensität ist mehrfach so gross wie die einer Permanganatlösung gleicher Konzentration.

Der rote Körper fällt amorph an; es gelang nicht, ihn aus irgendeinem Lösungsmittel kristallin zu erhalten. Zur Analyse mussten wir uns deshalb chromatographischer Methoden und der Hochspannungs-Papierelektrophorese bedienen.

Eine Erklärung für die Entstehung des Farbstoffes bot die Annahme, dass das Glycylbenzimid (I) unter Wasserabspaltung Ringschluss erleidet zum 2-Phenyl-imidazolon-4(5) (II). Die grosse formale Ähnlichkeit dieser Verbindung mit Indoxyl legt die Vermutung nahe, dass auch hier leicht Oxydation eintreten könne unter Bildung der indigoiden Verbindung (III), die 1900 von Ruhemann und Stapleton[2] aus

[1] Th. Wieland und H. J. Hennig, *Chem. Ber.* **93**, 1236 (1960).
[2] S. Ruhemann und H. E. Stapleton, *J. Chem. Soc.* **77**, 804 (1900).

Acetylendicarbonsäure-bzw. Chlorfumarsäure-diäthylester und Benzamidin hergestellt und "glyoxaline red" genannt wurde.

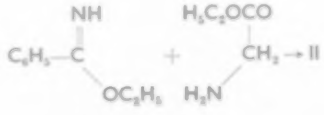


I II III

Charakteristisch für das "Glyoxalinrot" ist die sehr leicht durch Kochen mit Eisessig erfolgende Umwandlung in eine gelbe, gut kristallisierende Substanz, die unter Aufnahme von einem Mol Wasser entstanden ist und nach Ruhemann und Stapleton die Konstitution (IV) besitzt.* Wir fanden, dass die Umwandlung auch in wasserhaltigem Phosphorsäure-tris-dimethylamid beim Erwärmen vor sich geht.

IV

Das hier zur Erklärung der Farbstoffbildung postulierte farblose 2-Phenyl-imidazolon-4(5) (II) wurde 1953 von Kjaer[3] aus Benziminoäthylester und Glycinäthylester, nach einer Methode, die schon 1907 von H. Finger angegeben worden war, hergestellt:



Finger hatte es, allerdings nicht in reiner Form, in Händen und beobachtete eine tiefe Rotfärbung seiner Lösung in Eisessig. Er nahm an, dass aus dem Imidazolon das Ruhemannsche Glyoxalinrot (III) entstanden war und wollte die Identität der Farbstoffe beweisen.[4] Die angekündigte Arbeit ist nicht erschienen; dafür berichtete Kjaer[3], dass beim Durchleiten von Luft durch eine Lösung des 2-Phenyl-imidazolons in Eisessig das Glyoxalinrot entstünde.

Bei einem Vergleich des Ruhemannschen Farbstoffes mit dem von uns aus Glycylbenzimid-hydrobromid erhaltenen stellten wir fest, dass es sich um verschiedene Stoffe handelt, wenn sie auch in den Farbstoffeigenschaften, der Alkalilöslichkeit, der Empfindlichkeit gegen naszierenden Wasserstoff übereinstimmen. So erfährt nur das Glyoxalinrot beim Kochen in Eisessig oder Phosphorsäure-tris-dimethylamid eine Umwandlung; es ist in jedem nicht-basischen Lösungsmittel schwerlöslich und wandert bei der Papierelektrophorese erst bei $p_H 12$, und zwar zur *Anode*. Der aus Glycylbenzimid entstehende Farbstoff dagegen bleibt in alkalischem und neutralem

* Sie lässt sich aus der prozentualen Zusammensetzung ableiten, ist aber nicht durch irgendwelche Reaktionen gesichert.

[3] A. Kjaer, *Acta Chem. Scand.* **7**, 1030 (1953).
[4] H. Finger, *J. Prakt. Chem.* **76**, 94 (1907).

Medium liegen, während er von $p_H 4$ ab, mit steigender H^+-Ionenkonzentration immer besser, unter Aufspaltung in mehrere rote Banden zur *Kathode* wandert. Es handelt sich also um ein Gemisch mässig basischer roter Stoffe. Ihre Anzahl hängt von den Darstellungsbedingungen ab. Auch ein am Start zurückbleibender gelbroter Rückstand enthält kein Glyoxalinrot, was sich durch Betupfen mit konz. Ammoniak zeigen lässt: Die Farbe bleibt unverändert, während das Papier sonst an Stellen, die den Ruhemannschen Farbstoff in kleinster Konzentration enthalten, violett wird.

Eine rasche Feststellung des günstigsten p_H-Bereichs für die pherographische Untersuchung gelang mit Hilfe des Lindsay–Johnsonschen Universalpuffers,[5] der durch allmähliche Zugabe von Natronlauge zu einer Stammlösung von Zitronensäure, Borsäure, primärem Kaliumphosphat und Veronal in Wasser eine sukzessive Erhöhung des p_H-Wertes von 2,6 bis 12 gestattet, die in Tabellen normiert ist.

Schwierigkeiten verursachte die Schwerlöslichkeit der aus Glycylbenzimid gewonnen roten Stoffe in den üblichen sauren, stark wasserhaltigen Puffern. Eine befriedigende Lösung bot die Verwendung zweier Puffersysteme, die auch die pherographische Untersuchung anderer schwerlöslicher Stoffe, soweit sie mit Protonen reagieren, ermöglichen dürften: Ameisensäure-Eisessig-Wasser-Dimethylformamid 20:13:40:40 (p_H 1,8) und Ameisensäure-Wasser-Dimethylformamid 9:15:16 (p_H 1,9). Der Gehalt von rund 40% Dimethylformamid setzt die Azidität genügend herab und erhöht zugleich die Löslichkeit so weit, dass eine einwandfreie Trennung möglich wird.

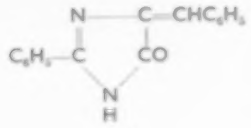
Wir haben mit Hilfe dieser Technik das aus dem 2-Phenylimidazolon-4(5) nach Finger[4] und Kjaer[3] entstehende rote Produkt pherographisch untersucht. Dabei fanden wir, dass es sich um eine ganze Reihe roter Substanzen handelt, die sich durch ihre Wanderungsgeschwindigkeit zur Kathode hin unterscheiden. Dagegen liess sich, entgegen den Angaben Kjaers, kein Ruhemannsches Glyoxalinrot nachweisen. Die Vermutung, dass wenigstens einige der roten Stoffe aus dem Phenylimidazolon (II) mit den aus Glycylbenzimid entstehenden identisch sind, bestätigte sich: Je zwei wiesen im Papierchromatogramm (Lösungsmittel sek. Butanol/Ameisensäure/Wasser 15:3:2) praktisch gleiche R_f-Werte auf, und die U.V.-Spektren der mit Dimethylformamid eluierten Banden waren identisch. Damit war schon der Beweis erbracht, dass die Bildung der roten Farbstoffe aus Glycylbenzimid über das 2-Phenylimidazolon-4(5) verläuft. Trotzdem wurde sein direkter Nachweis versucht.

Bei seiner Unbeständigkeit war eine Isolierung unter den Bedingungen der Farbstoffbildung nicht möglich. Wir versuchten deshalb, das Imidazolon abzufangen, bevor es zu den roten Produkten weiterreagiert. Das gelang mit Benzaldehyd: Beim Erwärmen einer wässrigen Lösung von Glycylbenzimid-hydrobromid mit dem Aldehyd tritt nur eine schwache Rotfärbung auf; dafür fällt eine gelbe Verbindung aus, die durch Mischschmelzpunkt, I.R.-Spektrum und ihre charakteristische Fluoreszenz in alkoholischer Natronlauge als 2-Phenyl-4(5)-benzyliden-imidazolon-5(4) (V) identifiziert wurde. Diese Verbindung war von Erlenmeyer[6] aus dem Amid der Benzoylaminozimtsäure, von Ekeley und Ronzio[7] aus Benzamidin, Glyoxal und Benzaldehyd*

* Ekeley und Ronzio hielten die Substanz für das isomere 2-Phenyl-4-benzoyl-imidazol. Williams *et al.* wiesen jedoch durch Hydrierung der C=C-Doppelbindung nach, dass es sich um die oben angegebene Substanz handelt.[8] Wir haben diesen Befund durch Vergleich der I.R.-Spektren bestätigen können.

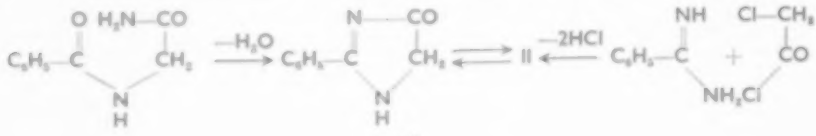
[5] W. C. Johnson und A. J. Lindsay, *Analyst* **64**, 490 (1939).
[6] E. Erlenmeyer, jr., *Ber. Dtsch. Chem. Ges.* **33**, 2036 (1900).
[7] J. B. Ekeley und A. R. Ronzio, *J. Amer. Chem. Soc.* **57**, 1353 (1935).
[8] D. L. Williams, F. L. Symonds, J. B. Ekeley und A. R. Ronzio, *J. Amer. Chem. Soc.* **67**, 1157 (1945).

und von Kjaer[3] direkt aus dem 2-Phenyl-imidazolon-4(5) mit Benzaldehyd erhalten worden.



V

Wenn das Imidazolon (II) Zwischenprodukt der Farbstoffbildung ist, so sollten alle Reaktionen, die II ergeben, auch zur Bildung der basischen roten Farbstoffe führen. Deshalb wurde die intramolekulare Kondensation des Hippursäureamids-das entstehende Produkt (VI) wäre mit dem Imidazolon II tautomer- und der Aufbau des Fünfrings aus Benzamidin und Chloracetylchlorid versucht.



VI

Beim Hippuramid, das sich vom Glycylbenzimid formal nur durch die Vertauschung der Methylen- und Carbonylgruppe unterscheidet, muss die Mesomeriestabilisierung der Säureamide einen Ringschluss erschweren. Die Kondensation wurde, als Modell einer Polypeptidanhydrisierung, von Karrer und Gränacher versucht.[9] Das Phenylimidazolon, das sie als weisse, sehr beständige Substanz beschreiben, und aus dem Miyamichi mit Glycerin und Bariumhydroxyd "proteinähnliche" Produkte erhielt,[10] wurde jedoch von Kjaer[11] als Hippursäurenitril erkannt, das mit dem Phenylimidazolon die Summenformel gemeinsam hat.

Nach dem Erhitzen von Hippuramid mit Polyphosphorsäure gelang es uns, pherographisch die Bildung der roten Farbstoffe nachzuweisen. Im Gegensatz zum Glycylbenzimid-hydrobromid sind sie jedoch hier nicht durch thermische Zersetzung erhältlich, da dabei Verkohlung eintritt. In recht guter Ausbeute konnten wir sie aber aus Hippuramid durch Erhitzen auf 170° nach Zusatz basischer Stoffe wie Kaliumcarbonat oder Natriumacetat gewinnen. Die Farbstoffbildung aus Glycylbenzimid (I) wird durch Natriumacetat sehr erleichtert und gelingt dann schon bei 60°.

Die Reaktion von Chloracetylchlorid mit Benzamidin führt ebenfalls zu beträchtlichen Mengen des Farbstoffgemisches, von dem auch schon beim Erhitzen von Benzamidin-monochloracetat mit Natriumacetat kleine Mengen gebildet werden.

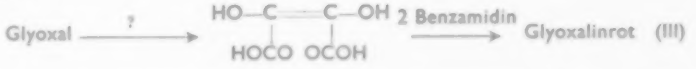
In diesem Zusammenhang erscheint eine Untersuchung von Ekeley und Ronzio[12] über rote Kondensationsprodukte aus Benzamidin und Glyoxal bemerkesnwert. Die Autoren erhielten das Ruhemannsche Glyoxalinrot aus einer Benzamidin-Glyoxal-Additionsverbindung durch Erhitzen in alkoholischer Natriumäthylatlösung. Ihr Farbstoff wird jedoch beim Kochen in Eisessig nicht gelb, sondern braunrot, und das Hydratationsprodukt färbt sich bei Zugabe von Alkalien, im Gegensatz zu dem nach Ruhemann und Stapleton hergestellten, sofort rot. In wässrig-alkalischer Lösung

[9] P. Karrer und Ch. Gränacher, *Helv. Chim. Acta* **7**, 765 (1924).
[10] E. Miyamichi, *J. Pharm. Soc. Japan* **50**, 1100 (1930); *Chem. Abstr.* **25**, 1247 (1931).
[11] A. Kjaer, *Acta Chem. Scand.* **3**, 647 (1949).
[12] J. B. Ekeley und A. R. Ronzio, *J. Amer. Chem. Soc.* **59**, 1313 (1937).

dagegen bildet sich aus Benzamidin und Glyoxal kein Glyoxalinrot, sondern eine ganze Reihe anderer roter Stoffe, von denen mindestens zwei mit von uns untersuchten identisch scheinen. Das Imidazolon (II) lässt sich auch hier durch Abfangen mit Benzaldehyd (s. Fussnote S. 2) nachweisen.

Wir haben das abweichende Verhalten des nach Ekeley und Ronzio hergestellten Hydratationsproduktes (IV) durch pherographische Untersuchung aufklären können. Neben dem Glyoxalinrot entstehen dort immer in kleiner Menge zwei rote Farbstoffe, die sich bei der Elektrophorese und im Chromatogramm wie die von uns hergestellten basischen verhalten. Sie werden durch die Behandlung mit Eisessig nicht verändert und färben die gelbe Verbindung IV braunrot an. Im Alkalischen erzeugen sie sofort die von den Autoren beschriebene tiefrote Farbe.

Bei keiner der von uns gefundenen Bildungsweisen roter Produkte liess sich Glyoxalinrot nachweisen; die ursprünglich vermutete oxydative Dimerisierung des 2-Phenyl-imidazolons-4(5) haben wir in keinem Fall feststellen können. Es ist deshalb auch nicht anzunehmen, dass das nach Ekeley und Ronzio aus Benzamidin und Glyoxal in absolut-alkoholischer Lösung erhältliche Glyoxalinrot durch Oxydation des Imidazolons (II) entsteht. Vielleicht wird es nach einem von den beiden Autoren vorgeschlagenen Mechanismus[12] aus Benzamidin und der nicht isolierten Oxalglykolsäure gebildet.



Die vorliegende Untersuchung zeigt, welche zentrale Stellung dem 2-Phenyl-imidazolon-4(5) (II) bei den auf so verschiedenen Wegen gewonnen roten Farbstoffen zukommt. Wir wissen allerdings noch nicht, wie diese farblose Verbindung zu den roten Produkten weiterreagiert. Das allgemeine Verhalten der Farbstoffe lässt auf gleiche Funktionen bei unterschiedlicher Molekülgrösse schliessen, was am leichtesten durch eine mehrfache Kondensation desselben Bausteins erklärt werden kann. Der Benzolring muss dabei eine entscheidende Rolle spielen, denn die entsprechenden Methyl- und Benzylimidazolone sind stabile Verbindungen, die keine Farbstoffe liefern.

Eine Sonderstellung nimmt ein nur in wässriger Lösung aus Glycylbenzimid-hydrobromid (I) entstehender, mehr violettroter, ebenfalls basischer Farbstoff ein, der bei keinem der anderen Verfahren auftritt. Durch Zugabe von Pyrrolidon wird seine Bildung sehr beschleunigt, und er erscheint dabei in Form mikroskopischer Kristalle mit grünem Oberflächenglanz, die kaum noch durch die anderen Farbstoffe verunreinigt sind.

BESCHREIBUNG DER VERSUCHE

Darstellung des roten Farbstoffgemisches

Aus Glycylbenzimid in wässriger Lösung. Eine Lösung von 2 g des Hydrobromids in 50 ml Wasser wird von etwa ungelösten Flocken abfiltriert und 15 Minuten auf dem Wasserbad erwärmt. Sie färbt sich dabei rot. Man lässt noch zwei Tage bei Raumtemperatur stehen, sammelt den schwarzroten, flockigen Niederschlag auf einem kleinen Filter und wäscht ihn mit Wasser, wenig Methanol und schliesslich mit Äther. Dann wird er in möglichst wenig Dimethylformamid gelöst und mit Petroläther wieder ausgefällt. Ausbeute: 30 mg.

Aus Glycylbenzimid durch Erhitzen mit Natriumacetat. 1 g des Hydrobromids wird mit der 2,5-fachen Menge wasserfreiem Natriumacetat fein verrieben und in einem Verbrennungsrohr kurze

Zeit auf 150° erhitzt. Die Masse färbt sich unter Schmelzen tiefrot. Sie wird noch heiss in möglichst wenig Methanol gelöst. Bei Zusatz von Wasser fällt das Farbstoffgemisch flockig aus. Man zentrifugiert den Niederschlag ab, wäscht mit viel Wasser, Alkohol und digeriert mit Äther. Eine weitere Reinigung ist durch Lösen in verdünnter Natronlauge und Ausfällen mit Säuren möglich. Man erhält so 120 mg.

Aus Hippursäureamid. Das Verfahren ist dasselbe wie beim Glycylbenzimid-hydrobromid, doch genügt hier, da das Amid neutral ist, die 1,5-fache Menge Natriumacetat. Das Reaktionsprodukt wird in Methanol gelöst, nach Zusatz von Wasser und etwas Essigsäure, die die Zusammenballung des Niederschlags erleichtert, abzentrifugiert und wie oben aufgearbeitet. Die Ausbeute ist etwas geringer als bei der Darstellung aus Glycylbenzimid-hydrobromid.

Aus Benzamidin und Chloracetylchlorid. Aus einer konzentrierten wässrigen Lösung von Benzamidin-hydrochlorid wird die Base mit Natronlauge in Freiheit gesetzt. Es muss ein Überschuss an NaOH vorhanden sein. Man schüttelt gut durch und versetzt die Emulsion tropfenweise mit der berechneten Menge Chloracetylchlorid. Unter starker Erwärmung färbt sich die Lösung tiefrot. Nach dem Abkühlen wird mit verdünnter Salzsäure schwach angesäuert, der Niederschlag abzentrifugiert, mit viel Wasser gewaschen, getrocknet und mit Äther digeriert. Aus 1 g Benzamidin können etwa 100 mg Farbstoffgemisch gewonnen werden.

2-*Phenyl*-4(5)-*benzyliden*-*imidazolon*-5(4). 1 g Glycylbenzimid-hydrobromid wird in 10 ml Wasser gelöst, die filtrierte Lösung mit 0,5 g Benzaldehyd versetzt und gut durchgeschüttelt. Sie färbt sich dabei rotorange. Man erhitzt 10 Minuten auf dem Wasserbad, lässt abkühlen, filtriert den voluminösen Niederschlag ab und wäscht den überschüssigen Benzaldehyd mit viel Äther heraus. Das Glyoxalidonderivat wird zweimal aus n-Butanol umkristallisiert. Es schmilzt bei 270° zu einer roten Flüssigkeit und zeigt keine Schmelzpunktsdepression mit dem nach Lit.[8] oder Lit.[11] synthetisierten Produkt. (Gef. C 77,50; H 5,23; N 11,17; $C_{16}H_{12}ON_2$ erfordert C 77,39; H 4,87; N 11,28%).

Tetrahedron, 1961, Vol. 15, pp. 7 to 17. Pergamon Press Ltd. Printed in Northern Ireland

DIE REAKTION VON 2.6-DIMETHYLNAPHTHALIN MIT DIAZOESSIGESTER

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Zusammenfassung—Die Thermolyse des Diazoessigesters in 6 Moläquival. 2.6-Dimethylnaphthalin ergibt 58% d.Th. Carbäthoxycarben-Monoaddukt, das 74% des 2.6-Dimethyl-1a.7b-dihydro-1H-cyclopropa[a]naphthalin-carbonsäure-(1)-äthylesters (VI), 15% der isomeren 1b.5-Dimethylverbindung VIII und 9% 2.7-Dimethyl-5H-benzocycloheptencarbonsäure-(6)-äthylester (X) enthält; daneben treten 11% Diaddukt XXIV auf. Die Produkte werden, vornehmlich durch Oxydation und Hydrierung, konstitutionell geklärt und spektral charakterisiert. Die partiellen Geschwindigkeitskonstanten der Carbäthoxycarben-Anlagerung, bezogen auf die 1.2-Bindung des Napthalins = 1.0, betragen für die 1.2- und 3.4-Bindung des 2.6-Dimethylnaphthalins 1.4 bzw. 4.2.

Abstract—Thermal decomposition of ethyl diazoacetate in 6 molar equivalents of 2.6-dimethylnaphthalene yielded 58 per cent of carbethoxycarbene monoadducts which comprise 74 per cent ethyl 2.6-dimethyl-1a.7b-dihydro-1H-cyclopropa[a]naphthalene-(1)-carboxylate (VI), 15 per cent of the isomeric 1b.5-dimethyl compound VIII and 9 per cent of ethyl 2.7-dimethyl-5H-benzocycloheptene-(6)-carboxylate (X). The higher boiling fraction of the product contained 11 per cent of diadduct XXIV. These compounds were structurally elucidated, especially by oxidation and hydrogenation, and were characterised by U.V. and I.R. spectra. The partial rate factors of carbethoxycarbene addition, with reference to the 1.2-bond of naphthalene taken as 1.0, were 1.4 for the 1.2-bond and 4.2 for the 3.4-bond of 2.6-dimethylnaphthalene.

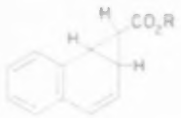
BEI der Anlagerung des Methylens oder Carbäthoxymethylens an geometrisch-isomere Alkene bleibt deren konfigurative Beziehung erhalten.[2] Diese *cis*-Addition der Carbene ist mit einem Dreizentren-Mechanismus plausibel zu deuten. Auch über den Einfluss von Substituenten auf die Reaktivität der olefinischen Doppelbindung gegenüber Carbenen ist einiges bekannt.[3]

Von der Umsetzung der Carbene mit der *aromatischen* CC-*Bindung* weiss man viel weniger, obwohl die klassische Untersuchung der Reaktion des Benzols mit Diazoessigester bereits 75 Jahre zurückliegt.[4] Die Vielzahl der Produkte bereitet schon bei der Klärung der Reaktionen des Diazoessigesters mit monosubstituierten Benzolen grosse Schwierigkeiten. Dabei vermag sich die Primäraddition des Carbäthoxycarbens an 3 verschiedenen CC-Bindungen zu vollziehen;[5] der Übergang in doppelbindungsisomere substituierte Cycloheptatriene sowie der Angriff des Carbens auf Alkylseitenketten bedeuten zusätzliche Komplikationen. Über den bevorzugten Angriffsort des Carbäthoxycarbens auf polycyclische Aromaten liegen Informationen vor.[6]

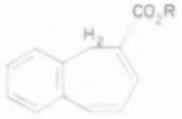
[1] Aus der Dissertation G. Juppe, Universität München (1958).
[2] P. S. Skell und R. C. Woodworth, *J. Amer. Chem. Soc.* **78**, 4496 (1956); W. v. E. Doering und P. La Flamme, *Ibid.* **78**, 5447 (1956); W. v. E. Doering und T. Mole, *Tetrahedron* **10**, 65 (1960).
[3] P. S. Skell und A. Y. Garner, *J. Amer. Chem. Soc.* **78**, 5430 (1956); W. v. E. Doering und W. A. Henderson, *Ibid.* **80**, 5274 (1958); P. S. Skell und R. M. Etter, *Chem. & Ind.* 624 (1958).
[4] E. Buchner und Th. Curtius, *Ber. Dtsch. Chem. Ges.* **18**, 2379 (1885); E. Buchner, *Ibid.* **30**, 632 (1897).
[5] K. Alder, R. Muders, W. Krane und P. Wirtz, *Liebigs Ann.* **627**, 59 (1959).
[6] N. L. Drake und T. R. Sweeney, *J. Org. Chem.* **11**, 67 (1946); G. M. Badger, J. W. Cook und A. R. M. Gibb, *J. Chem. Soc.* 3456 (1951); M. J. S. Dewar und C. R. Ganellin, *J. Chem. Soc.* 3139 (1959).

Der Einfluss von Substituenten auf die Reaktionsbereitschaft der CC-Bindung des Benzols gegenüber Carbäthoxycarben wurde noch nicht untersucht. Die hier allein mögliche Konkurrenzmethode scheitert an den analytischen Schwierigkeiten. Das Naphthalinsystem bietet für die Untersuchung des Substituenteneinflusses Vorteile.

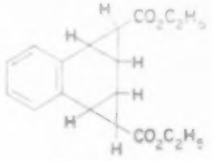
Buchner und Hediger[7] formulierten das Hauptprodukt aus Naphthalin und Diazoessigester als 2.3-Benzo-norcaradien-(2.4)-carbonsäure-(7)-äthylester (I). Huisgen und Juppe[8] bestätigten die Konstitution mit neuen chemischen und spektralen Befunden. Eine Isomerisierung zum 5H-Benzocyclohepten-carbonsäure-(6)-äthylester[9] (III) findet erst bei 260° statt. Bei der Thermolyse des Diazoessigesters in 5 Moläquival. Naphthalin wurden 52% d.Th. I und 14–17% d.Th. zweier diastereomerer Diaddukte V erhalten;[8] I und V machen nahezu 95% des hochvakuumflüchtigen Produkts aus.



I R = C_2H_5
II R = H

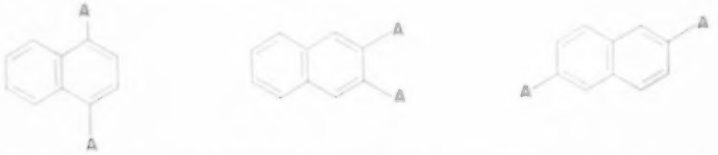


III R = C_2H_5
IV R = H



V

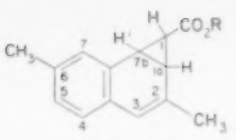
Da die Reaktivität des Naphthalins auf die 1.2-Bindung beschränkt ist, lassen eine Reihe disubstituierter Naphthaline, z.B.



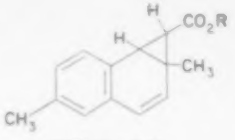
nur jeweils 2 isomere Carbäthoxycarben-Addukte erwarten. Die Analyse solcher Isomerengemische erlaubt es, die intramolekulare Konkurrenz substituierter und unsubstituierter Bindungen zahlenmässig zu erfassen. Der intermolekulare Konkurrenzversuch mit Napthalin sollte dann die Ermittlung partieller Geschwindigkeitskonstanten der aromatischen Bindungen ermöglichen. Hier sei die Umsetzung des Diazoessigesters mit 2.6-Dimethylnaphthalin beschrieben.

Bei der Thermolyse in 6 Moläquival. des Kohlenwasserstoffs bei 140–145° gelangten wir zu 58% d.Th. an destilliertem Rohester, dessen Gehalt an den 3 Komponenten VI, VIII und X laut quantitativer IR-Analyse 74, 15 und 9% betrug; 98% des Rohesters sind somit erfasst. Eine Umsetzung der Methylgruppen des 2.6-Dimethylnaphthalins mit Carbäthoxycarben[10] haben wir nicht beobachtet. Trotz des Kohlenwasserstoffüberschusses trat das Carbäthoxycarben erneut mit der olefinischen Doppelbindung von VI und VIII in Reaktion; 11% d.Th. Diaddukt XXIV fielen als Rohdestillat an.

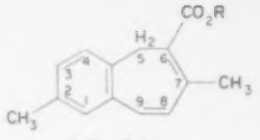
[7] E. Buchner und St. Hediger, *Ber. Dtsch. Chem. Ges.* **36**, 3502 (1903).
[8] R. Huisgen und G. Juppe, *Chem. Ber.* **94**, im Druck.
[9] Nomenklatur und Bezifferung folgen den Richtlinien des Ring Index, 2.Aufl., Amer. Chem. Soc. (1960).
[10] E. Buchner und P. Schulze, *Liebigs Ann.* **377**, 259 (1910) isolierten etwas *p*-Methyl-hydrozimtsäure aus *p*-Xylol und Diazoessigester. L. I. Smith und P. O. Tawney, *J. Amer. Chem. Soc.* **56**, 2167 (1934), erhielten 30% Trimethyl-hydrozimtsäure aus Durol und Diazoessigester.



VI R = C_2H_5
VII R = H

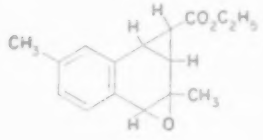


VIII R = C_2H_5
IX R = H

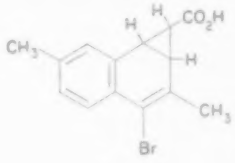


X R = C_2H_5
XI R = H

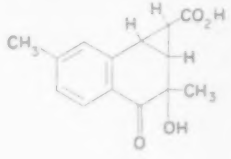
Aus dem destillierten Ester schied sich bei längerem Stehen das kristalline Hauptprodukt VI ab. Die U.V.-Spektren von VI und VII entsprechen wie die von I und der zugehörigen Carbonsäure II dem 1.2-Dihydronaphthalin-Typ; für eine charakteristische bathochrome Verschiebung der Bandenmaxima dürfte die schwache Konjugationsbeziehung des Cyclopropanringes mit dem aromatischen Kern verantwortlich sein[8]. Im Gegensatz zu II[8] nahm VII keinen katalytisch erregten Wasserstoff auf. Jedoch wiesen der Verbrauch von 1 Äquival. Perbenzoesäure nebst Isolierung des Epoxyds XII aus VI auf *eine* olefinische Doppelbindung hin. Das Dibromid von VII verlor schon gegen 100° Bromwasserstoff unter Bildung von XIII.



XII

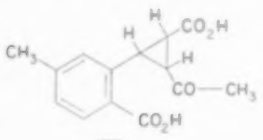


XIII

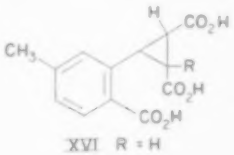


XIV

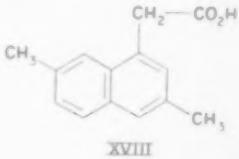
Die Oxydation erhellte die Stellung der Methylgruppen in VII. Mit Kaliumpermanganat in siedendem Aceton erhielten wir 49% der Ketol-carbonsäure $C_{14}H_{14}O_4$ (XIV) und 15% der Ketodicarbonsäure XV, die beide Carbonylderivate liefern. Die Ozonisation von VII in Essigester ergab gar 79% der Ketodicarbonsäure $C_{14}H_{14}O_5$ (XV). Dass in XV ein *Methylketon* vorliegt, daran liess die Jodoformreaktion keinen Zweifel; die Tricarbonsäure XVI liess sich dabei zu 82% isolieren. Die Einwirkung von Natriumhypochlorit auf XV führte zu einer Chlortricarbonsäure $C_{13}H_{11}ClO_6$ (XVII). Das Chlor befindet sich in aliphatischer Bindung; vermutlich geht die Chlorierung am Cyclopropanring der Chloralspaltung zum Carboxylat voraus.



XV



XVI R = H
XVII R = Cl



XVIII

Diese Befunde sind nur mit der Formulierung des Hauptprodukts als 2.6-Dimethyl-1a.7b-dihydro-1H-cyclopropa[a]naphthalin-carbonsäure-(1)-äthylesters (VI)[9] vereinbar. In siedendem Acetanhydrid in Gegenwart von Schwefelsäure isomerisiert sich die Carbonsäure VII zur noch nicht beschriebenen 2.6-Dimethyl-naphthyl-(4)-essigsäure (XVIII) in 85% Ausbeute. Aus der Analogie mit der Bildung von α-Naphthylessigsäure aus II[8] unter gleichen Bedingungen sowie aus der spektralen Ähnlichkeit mit 2.6-Dimethylnaphthalin (Fig. 1) erschliessen wir die Konstitution von XVIII.

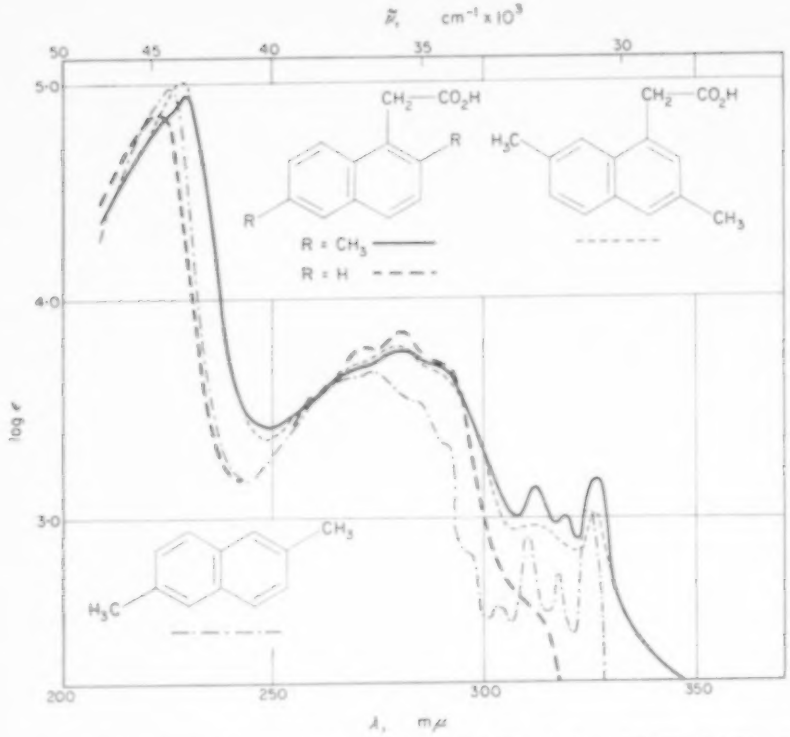
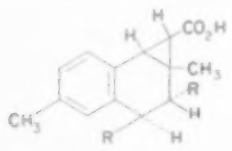
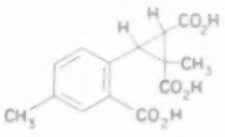


FIG. 1. U.V.-Absorption von 2.6-Dimethyl-naphthyl-(4)-essigsäure (XVIII), 2.6-Dimethyl-naphthyl-(1)-essigsäure (XXII), α-Naphthylessigsäure und 2.6-Dimethylnaphthalin in 96-proz. Alkohol.

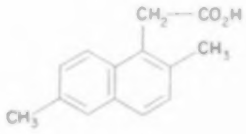
Die Isolierung der zweiten Säure (IX) aus dem Rohester war mühsam und verlustreich. Im Einklang mit der Erwartung vollzog sich die alkalische Hydrolyse des Äthylesters VIII langsamer als die von VI. Im Anschluss an die fraktionierte Verseifung wurde der zuletzt freigesetzte Säureanteil als Kaliumsalz gefällt; die fraktionierte Kristallisation der Carbonsäure aus Methanol erlaubte die Reindarstellung von IX.



XIX R = H
XX R = Br



XXI



XXII

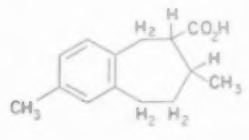
Im Gegensatz zu VII nahm IX 1 Mol Wasserstoff in Gegenwart von Platin auf unter Bildung von XIX. Das Dibromid XX enthält kein Brom am tert. Kohlenstoff und ist daher stabiler als das sich von VII ableitende Derivat. Die Behandlung der Säure IX mit Ozon und anschliessend mit Wasserstoffperoxyd lieferte eine Tricarbonsäure (XXI) *ohne Kohlenstoffverlust;* die oxydativ gesprengte Doppelbindung muss also disekundär sein. Auch bei IX löste Acetanhydrid/Schwefelsäure eine Aromatisierung aus, die zu 2.4-Dimethyl-naphthyl-(1)-essigsäure (XXII) (Fig. 1) führte.

Diese wurde mit einem synthetischen Präparat, das aus 2.6-Dimethylnaphthalin über das 1-Chlormethyl-Derivat (allerdings nicht ganz rein) erhalten wurde, identifiziert. Alle diese Umsetzungen stützen die Konstitution VIII für das zweite Reaktionsprodukt.

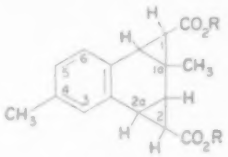
Auch die infraroten Carbonylschwingungen der Carbonsäure VII und IX bieten einen indirekten Beweis für das Benzo-norcaradien-Skelett. Mit 1676 bzw. 1678/cm liegt ihre Schwingungszahl zwischen denen konjugierter und nichtkonjugierter Carbonsäuren; eben das ist von Cyclopropan-carbonsäuren bekannt.[11]

Die Geschwindigkeit der Epoxydation der Olefine nimmt mit der Zahl der Alkylgruppen an der Doppelbindung zu.[12] Die Verfolgung des zeitlichen Ablaufs der Reaktion mit Perbenzoesäure bestätigte die Konstitutionen VII und IX. Unter Standardbedingungen (Chloroform, 0°) fanden wir nach 5 Stdn. folgenden Umsatz in Mol%: VII 44%, IX 27%. Der methylfreie Grundkörper II hatte unter gleichen Bedingungen erst zu 17% reagiert.

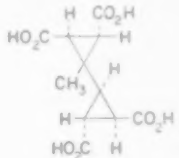
Während VI sich als bei 250° stabil erwies, erlitt der Äthylester VIII bei dieser Temperatur in guter Ausbeute eine Umlagerung zum Cycloheptatrien-Abkömmling X. Die infrarote CO-Bande der Säure XI bei 1675/cm zeigt eine konjugierte Carboxylgruppe an. Die katalytische Hydrierung der 2.7-Dimethyl-5H-benzocycloheptencarbonsäure-(6) (XI) ergab ein Tetrahydroderivat XXIII unter Verschiebung der Lichtabsorption nach kurzen Wellen (Fig. 2); mit 1686/cm lag die Carbonylbande von XXIII im Bereich des nichtkonjugierten Carboxyls. Die Lage der Doppelbindungen wurde in X wie bei dem konstitutionell gesicherten methylfreien Ester III,[8] der aus dem Grundkörper I bei 250° hervorging, angenommen. Die U.V.-Absorption der Carbonsäuren stützt diese klare Analogie.



XXIII



XXIV R = C_2H_5
XXV R = H



XXVI

Der ringerweiterte Ester X ist identisch mit dem dritten Produkt aus Diazoessigester und 2.6-Dimethylnaphthalin (S. p. 8). Wir halten es für möglich, dass X dort nicht als Primär-, sondern als Sekundärprodukt auftritt und aus der thermischen Isomerisierung von VIII bei der Aufarbeitung hervorgeht. Mit dieser Annahme ändert sich die Bilanz; die Primärprodukte VI und VIII entstehen nun im Verhältnis 3:1. Warum übrigens der isomere Ester VI die Ringerweiterung nicht, zumindest noch nicht bei 250°, eingeht, vermögen wir nicht zu sagen.

Die schon S. p. 8 erwähnte, höhersiedende Fraktion aus Diazoessigester und 2.6-Dimethylnaphthalin enthält das Diatddukt XXIV. Aus dem entsprechenden Naphthalin-diaddukt V isolierten wir 2 Carbonsäuren, die wir als *cis-trans*-Isomere bezüglich der Angliederung der beiden Cyclopropanringe ansprechen.[8] Vermutlich handelt es

[11] Vgl. R. J. Mohrbacher und N. H. Cromwell, *J. Amer. Chem. Soc.* **79**, 401 (1957).
[12] H. Meerwein, A. Ogait, W. Prang and A. Serini, *J. Prakt. Chem.* [2], **113**, 9 (1926); J. Böeseken und J. Stuurman, *Rec. Trav. Chim. Pays-Bas* **56**, 1034 (1937). Übersicht bei D. Swern, *Chem. Rev.* **45**, 1, 48 (1949).

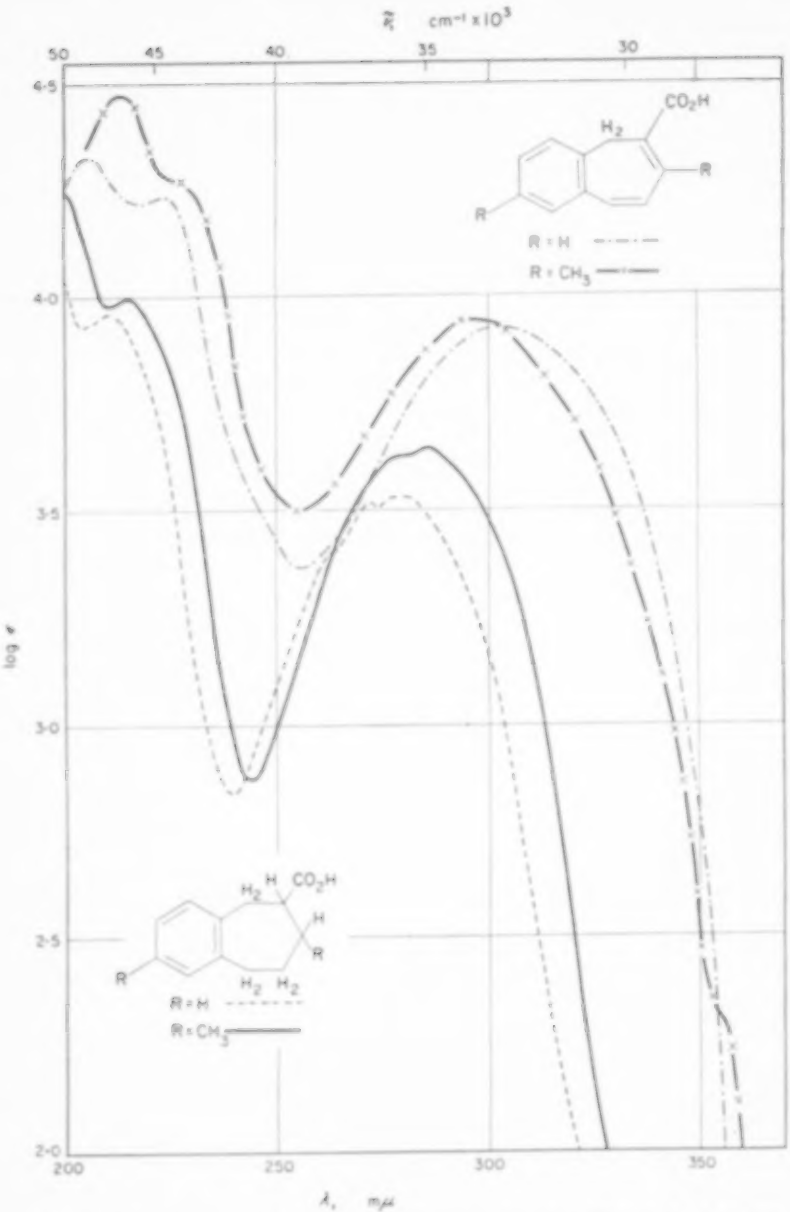


FIG. 2. U.V.-Absorption der 5H-Benzocyclohepten-carbonsäure-(6) (IV), der 2.7-Dimethyl-5H-benzocyclohepten-carbonsäure-(6) (XI), der 6.7.8.9-Tetrahydro-5H-benzocyclohepten-carbonsäure-(6) (XXIII, H statt CH_3) und der 2.7-Dimethyl-6.7.8.9-tetrahydro-5H-benzocyclohepten-carbonsäure-(6) (XXIII) in 96-proz. Äthanol.

sich bei der Dicarbonsäure XXV, die aus der alkalischen Hydrolyse von XXIV hervorging, um die *trans*-Verbindung. Die Resistenz von XXV gegenüber Permanganat und Brom zeigt die Abwesenheit von Doppelbindungen. Die durchgreifende Ozonisation lieferte 1-Methyl-bicyclopropyl-tetracarbonsäure-(2.3.2′.3′) (XXVI).

Soweit man aus den Ausbeuten an den Estern VI und VIII (43% und 14%, bezogen auf Diazoessigester) schliessen darf, greift das Carbäthoxycarben die 1.2- und die 3.4-Bindung des 2.6-Dimethylnaphthalins im Verhältnis 1:3.1 an. Ein Konkurrenzversuch von Diazoessigester mit einem äquimolaren Gemisch von Naphthalin und 2.6-Dimethylnaphthalin ergab als vorläufiges Resultat eine um den Faktor 2.8 bevorzugte Anlagerung des Carbäthoxycarbens an 2.6-Dimethylnaphthalin. Die intra- und intermolekulare Konkurrenz erlaubt die Berechnung von *partiellen Geschwindigkeitskonstanten*, bezogen auf *eine* Naphthalin-1.2-Bindung = 1.0:

1.2-Bindung des 2.6-Dimethylnaphthalins $k_p = 1{\cdot}4$

3.4-Bindung des 2.6-Dimethylnaphthalins $k_p = 4{\cdot}2$

Die Methylgruppen führen dem Naphthalinkern Elektronen zu und erhöhen damit die Reaktivität gegenüber Carbäthoxymethylen. Diese Steigerung ist aber bei der unsubstituierten Bindung des 2.6-Dimethylnaphthalins merklich stärker als bei der methylierten. Eine *sterische* Beeinträchtigung der Addition bietet eine plausible Erklärung. Eine solche Behinderung wurde auch von K. Alder[5] bei der Analyse der aus Toluol und den Xylolen erhaltenen Produkte konstatiert.

EXPERIMENTELLER TEIL

2.6-Dimethylnaphthalin und Diazoessigester

2.6-*Dimethylnaphthalin* (Ges. für Teerverwertung, Duisburg-Meiderich) wurde zweimal aus Methanol umkristallisiert und zur Entfernung von eventuellen Metallspuren im Schwertkolben bei 120–125°/14 Torr destilliert. 480 g des Kohlenwasserstoffs (3·08 Mol) wurden unter Stickstoff im Ölbad auf 140–145° erhitzt. Unter Rühren liessen wir 61·5 g Diazoessigsäure-äthylester (0·52 Mol) innerhalb 10 Stdn. eintropfen. Nach einer weiteren Stde. war die Freisetzung des Stickstoffs mit 0·51 Mol beendet. Das erkaltete gelbe Reaktionsgemisch nahmen wir in siedendem Methanol auf und saugten nach Erkalten vom abgeschiedenen 2.6-Dimethylnaphthalin ab. Weitere Anteile des Kohlenwasserstoffs wurden nach mehrfachem Einengen abgetrennt. Nach Entfernen des Solvens destillierten wir den gelbbraunen Rückstand aus dem Claisenkolben. Auf einen Vorlauf, der aus *Fumarsäure-diäthylester* und 2.6-Dimethylnaphthalin bestand, folgten bei 104–127°/0·004 Torr 73·0 g hellgelbes Öl (*Esterfraktion A*) und bei 127–180°/0·004 Torr 18·5 g zähen gelben Öls (*Esterfraktion B*).

Die Fraktion A zeigte bei der Behandlung von 2 mMol-Proben mit Brom in Eisessig und Rücktitration mit Thiosulfat 0·97 Äquival. olefinische Doppelbindung an. Beim Aufbewahren im Kühlschrank kristallisierte die *Esterfraktion A* teilweise. Nach Anreiben mit Petroläther (30–40°) und mehrstdg. Kühlen auf −60° wurde abgesaugt. Durch Wiederholung der Tieftemperaturkristallisation mit dem Mutterlaugenanteil liessen sich 45–55% des Rohesters A abscheiden. Nach mehrfachem Umlösen aus Petroläther schmolzen die farblosen Nadeln des 2.6-*Dimethyl*-1a.7b-*dihydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1)-*äthylesters* (VI) bei 73–74°.

($C_{16}H_{18}O_2$ (242·3) Ber.: C, 79·31; H, 7·49. Gef.: C, 79·47; H, 7·38).

Isolierung der 1a.5-*Dimethyl*-1a.7b-*dihydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1) (IX). 12·3 g Fraktion A (nach Abtrennen von VI) wurden mit 0·70 Moläquival. KOH in siedendem Methanol verseift und nach Abziehen des Methanols mit Wasser/Methylenchlorid aufgearbeitet. Die aus der wässrigen Phase mit HCl gewonnene Rohsäure enthielt VII angereichert. Der restliche Ester (3·6 g) wurde mit Überschuss KOH in Methanol verseift und ergab 2·9 g Carbonsäure mit Schmp. 135–138°. Diese wurde in 15 cm³ starker Kaliumcarbonatlösung heiss gelöst; beim Erkalten schieden

sich 1·45 g feinkristallinen, schwer filtrierbaren Kaliumsalzes ab. Die daraus freigesetzte Säure wurde häufig aus Methanol umkristallisiert, wobei als Spitzenfraktion schliesslich 0·34 g farbloser Spiesse der Säure IX mit Schmp. 170–171° anfielen (ca. 1·5% der Esterfraktion A). Der KBr-Pressling zeigte starke IR-Banden bei 1678/cm (Carbonyl), 1433, 1324, 1230, 876, 822, 801/cm.

($C_{14}H_{14}O_2$ (214·3) Ber.: C, 78·48; H, 6·58. Gef.: C, 78·84; H, 6·45.)

Isolierung der 2.7-*Dimethyl*-5H-*benzocyclohepten-carbonsäure*-(6)(XI). Aus 50 g Esterfraktion A wurden 21 g VII abgetrennt und der restliche Rohester mit 4 mal 0·2 Moläquival. KOH und schliesslich mit überschüssigem KOH in Methanol fraktioniert hydrolysiert. Aus der 1. und 2.Säurefraktion kam im wesentlichen VII; der 3. und 4.Anteil (8·9 g) liessen sich durch fraktionierte Kristallisation der Säuren aus Methanol in 4·39 g Carbonsäure VII und 0·21 g IX auftrennen. 6·1 g Rohsäure der 5.Fraktion schmolzen bei 113–139° und wurden aus Methanol fraktioniert kristallisiert, wobei 0·89 g der schwerlöslichen Carbonsäure XI (2·0% der Esterfraktion A) erhalten wurden, die Schmp. 186–189° zeigten und in der Mischung mit VII oder IX Schmp.-Depressionnen von über 30° aufwiesen. Nach mehrfachem Umlösen aus Methanol schmolzen die farbl. Nadeln bei 190–191°.

($C_{14}H_{14}O_2$ (214·3) Ber.: C, 78·48; H, 6·58. Gef.: C, 78·10; H, 6·73.)

Quantitative I.R.-Analyse der Esterfraktion A. Aus 10·5 g Rohester A wurden 5·10 g VI und 0·12 g Dimethylnaphthalin abgetrennt, wobei 5·17 g öliger Ester verblieben. Die Extinktionen des in 5-proz. Cyclohexanlösung mit 0·1 mm-Fixküvette und Lösungsmittelkompensation im zweiten Strahlengang aufgenommenen I.R.-Spektrums wurden mit denen der reinen Äthylester VI, VIII und X auf der Grundlage von Eichkurven verglichen. Die Banden bei 1320, 880 und 1110/cm erwiesen sich für die drei Ester spezifisch. Ein Gemisch von 49% VI, 29% VIII und 17% X, bezogen auf die Einwaage an Rohester, ergab ein identisches I.R.-Spektrum. Mit den üblichen Vorbehalten der I.R.-Analyse errechnet sich daraus ein Gehalt der Esterfraktion A von 74% VI, 15% VIII und 9% X.

Zur Kontrolle wurde eine Probe des Rohesters verseift und die Rohsäure in Chloroform auf den Gehalt an VII und IX mittels der Banden bei 867 und 1080/cm I.R.-analysiert; für XI fand sich keine spezif., durch das Solvens nicht gestörte Bande. Das Resultat weist auf 70% VII und 17% IX in der Rohsäure.

2.6-*Dimethyl*-1a.7b-*dihydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1) (VII)

Carbonsäure VII. 7·62 g Ester VI wurden mit 3 g KOH in 50 cm³ Methanol 4 Stdn. rückflussgekocht. Unbeschadet des abgeschiedenen Kaliumsalzes versetzten wir mit Wasser und zogen das Methanol bei 20° im Vak. ab. Mit HCl wurden 6·65 g Säure (98% d.Th.) mit Schmp. 189–191° erhalten. Nach mehrfachem Umlösen aus Methanol schmolzen die farblosen Spiesse der Carbonsäure VII bei 195–197°. Die Säure VII wurde nach mehrstdg. Kochen mit 60-proz. KOH unverändert zurückisoliert. Das I.R.-Spektrum (KBr-Pressling) weist neben der Carbonylschwingung bei 1676/cm folgende kräftigen Banden auf: 695, 813, 845, 954, 1210, 1304, und 1440/cm.

($C_{14}H_{14}O_2$ (214·3) Ber.: C, 78·48; H, 6·58. Gef.: C, 78·56; H, 6·43.)

Zur Prüfung auf mögliche Stereoisomerisierung bei der Verseifung wurde eine Probe von VII mit Äthanol und H_2SO_4 erneut verestert; im Schmp. und Mischschmp. identisch mit VI. Der *Ester* erwies sich bei 250° noch als stabil. I.R.-Spektrum (KBr-Pressling): CO-Bande bei 1710/cm, weitere Banden bei 752, 809, 821, 832, 866, 889, 917, 1016, 1177, 1290, 1304 und 1370/cm.

2.6-*Dimethyl*-3-*brom*-1a.7b-*dihydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1) (XIII). 0·50 g VII wurden mit Brom in Chloroform behandelt, bis keine Entfärbung mehr stattfand. Der Rückstand nach Entfernen des Solvens zeigte beim raschen Erhitzen Zers. P. 133–135°. Nach dem Umlösen aus Cyclohexan lag der Zers.P. tiefer; auch die CH-Analyse wies auf die beginnende HBr-Abspaltung. Nach mehrstdg. Erhitzen auf 120° war die Gasentwicklung abgeschlossen. Aus Cyclohexan/Essigester kamen farbl. Nadeln mit Schmp. 208–209°.

($C_{14}H_{13}BrO_2$ (293·2) Ber.: C, 57·35; H, 4·47. Gef.: C, 57·53; H, 4·64.)

2.3-*Oxido*-2.6-*dimethyl*-1a.2.3.7b-*tetrahydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1)-*äthylester* (XII). 2·0 g VI wurden mit 110 Mol% Perbenzoesäure in 20 cm³ Chloroform 6 Tage bei −12° aufbewahrt. Nach Ausziehen der Benzoesäure mit Sodalösung und Entfernung des Chloroforms kristallisierte der Rückstand aus Äther/Petroläther. Mehrfaches Umlösen aus dem gleichen Mittel sowie aus Cyclohexan ergab farbl. Stäbchen mit Schmp. 112–113°.

($C_{16}H_{18}O_3$ (258·3) Ber.: C, 74·39; H, 7·02. Gef.: C, 74·50; H, 7·10.)

Zur quantitativen, zeitlichen Verfolgung der Epoxydation wurde eine Lösung von 1·27 mMol Perbenzoesäure in 17 cm³ frisch gereinigtem Chloroform bereitet (0·075 mMol/ccm). Sofort nach

Zusatz von 272 mg VII (1·27 mMol) bei 0° wurde die erste 1 cm³-Probe entnommen und der Persäuregehalt wie üblich[13] jodometrisch titriert. Aus der bei 0–1° verschlossen aufbewahrten Lösung wurden innerhalb 15 Stdn. 6 weitere Proben pipettiert; die Abnahme des Thiosulfattiters zeigte den Verbrauch an Persäure an.

2-*Hydroxy*-2.6-*dimethyl*-3-*oxo*-1a.2.3.7b-*tetrahydro*-1H-*cyclopropa*[a]*naphthalin*-*carbonsäure*-(1) (XIV). 2·05 g VII wurden in 50 cm³ stabilem Aceton in der Siedehitze spatelspitzenweise mit gepulv. Kaliumpermanganat versetzt, bis die violette Farbe bestehen blieb. Nach Reduktion mit schwefliger Säure und Abziehen des Acetons im Vak. schieden sich 1·15 g farbl. *Ketol* XIV (49% d. Th.) mit Schmp. 186–189° aus. Umlösen aus Benzol führte zu Nadeln mit Schmp. 202–203°.

($C_{14}H_{14}O_4$ (246·2) Ber.: C, 68·28; H, 5·73; Säureäquival. 252. Gef.: C, 67·90; H, 5·83; Säureäquival. 246.)

Aus der wässr. Mutterlauge von XIV kristallisierten nach längerem Stehen 0·37 g der *Ketodicarbonsäure* XV (15% d.Th.) mit Schmp. 225–231°.

Die Ketogruppe in XIV lässt sich durch Bildung eines 2.4-*Dinitrophenylhydrazons* nachweisen; aus Äthanol orangerote feine Nadeln mit Zers.-P. 245–246°. Das *Semicarbazon* kam aus Alkohol/Wasser und zeigte Zers.-P. 194–195°.

2-[2′-*Carboxy*-5′-*methyl*-*phenyl*]-3-*acetyl*-*cyclopropan*-*carbonsäure*-(1) (XV). 2·57 g VII wurden in 50 cm³ Essigester bei Raumtemp. mit einem 4-proz. Ozonstrom in 30-proz. Überschuss behandelt. Der Essigester wurde nach Zusatz von 2·65 g Natriumcarbonat in 20 cm³ Wasser im Vak. entfernt. Das amorphe Ozonid ging beim Erwärmen auf dem Wasserbad rasch in Lösung. Nach 1 Stde. bei 90° liessen wir erkalten und säuerten an: 2·48 g *Ketodicarbonsäure* XV (79% d.Th.), die nach Umlösen aus Essigester und aus Benzol/Methanol bei 252–253° schmolz.

($C_{14}H_{14}O_5$ (262·3) Ber.: C, 64·11; H, 5·38. Säureäquival. 131. Gef.: C, 63·52; H, 5·48. Säureäquival. 127.)

Das 2.4-*Dinitrophenylhydrazon* von XV zeigte nach Umkristallisieren aus Dioxan/Äthanol Zers.-P. 282–283°. Das *Semicarbazon* von XV wurde zunächst aus Alkohol/Wasser, dann mehrfach aus Essigester/Cyclohexan umgelöst; farbl. Nadeln mit Zers.-P. 198–199°.

($C_{15}H_{17}N_3O_5$ (319·3) Ber.: C, 56·42; H, 5·37. Gef.: 55·87; H, 5·58.)

1-[2′-*Carboxy*-5′-*methyl*-*phenyl*]-*cyclopropan*-*dicarbonsäure*-(2.3) (XVI). 145 mg Ketodicarbonsäure XV wurden in 5 cm³ Dioxan mit 1·0 cm³ 10-proz. NaOH und Jod-Jodkali versetzt, bis die Jodfarbe bestehen blieb. Nach 15 Stdn. bei Raumtemp. wurde das Jodoform abgesaugt (Mischprobe) und das Filtrat mit Schwefelsäure und schwefliger Säure angesäuert; bei zweitägigem Aufbewahren im Kühlschrank schieden sich 120 mg *Tricarbonsäure* XVI (82% d.Th.) in farbl. Drusen ab, die nach Umkristallisieren aus Methanol/Benzol Zers.-P. 285–286° aufwiesen.

($C_{13}H_{12}O_6$ (264·2) Ber.: C, 59·07; H, 4·58. Säureäquival. 88·1. Gef.: C, 58·18; H, 4·59. Säureäquival. 87·4.)

1-[2′-*Carboxy*-5′-*methyl*-*phenyl*]-2-*chlor*-*cyclopropan*-*dicarbonsäure*-(2.3) (XVII). In die Lösung von 3·6 g NaOH in 20 cm³ Wasser wurde bei 0° Chlor bis zur Lackmus-Neutralität eingeleitet. Nach Zugabe von weiteren 0·6 g NaOH und 2·20 g Ketodicarbonsäure XV erwärmten wir je 1 Stde. auf 60° bzw. 80°. Beim Ansäuren der erkalteten Lösung fielen 1·46 g Chlortricarbonsäure XVII (58% d.Th.) aus, die nach Umlösen aus Benzol/Methanol und aus Essigester bei 258–259° schmolz; farbl. Drusen. Die Verseifungsprobe mit KOH in Äthanol wies Chlor in aliphat. Bindung nach.

($C_{13}H_{11}ClO_6$ (298·7) Ber.: C, 52·24; H, 3·71. Säureäquival. 99·5. Gef.: C, 52·57; H, 3·96. Säureäquival. 98·0.)

2.6-*Dimethyl*-*naphthyl*-(4)-*essigsäure* (XVIII). 2·20 g VII wurden mit 10 cm³ Acetanhydrid in Gegenwart von einigen Tropfen konz. H_2SO_4 4 Stdn. rückflussgekocht. Nach Erkalten vollzog sich auf Zusatz von 20 cm³ Wasser hin in wenigen Min. die Hydrolyse des Anhydrids. Es schieden sich 1·86 g XVIII (85% d.Th.) aus; nach mehrfachem Umlösen aus Äthanol/Wasser zeigten die farbl. Nadeln Schmp. 158–160°. Die Titration mit n/10 NaOH in Alkohol gegen Phenolphthalein ergab ein Säureäquival. 214 (Ber. 214).

Der mit Äthanol/HCl aus XVIII bereitete *Äthylester* kristallisierte aus Petroläther in farbl. Nadeln mit Schmp. 72–73°.

($C_{16}H_{18}O_2$ (242·3) Ber.: C, 79·31; H, 7·49. Gef.: C, 78·97; H, 7·66.)

[13] G. Braun, *Org. Synth.*, Coll. Vol. I, p. 431, Note 9. John Wiley, New York (1943).

1a-5-*Dimethyl*-1a.7b-*dihydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1) (IX)

Äthylester (VIII). Aus Petroläther (30–40°) lange Nadeln mit Schmp. 74–75°. Der KBr-Pressling zeigte das Estercarbonyl bei 1728/cm und weitere starke IR-Banden bei 804, 877, 1030, 1153, 1200 und 1328/cm; die aromat. Ringschwingungen bei 1500 und 1603/cm sind nur schwach.

($C_{16}H_{18}O_2$ (242·3) Ber.: C, 79·31; H, 7·49. Gef.: C, 79·18; H, 7·59.)

1a.5-*Dimethyl*-1a.2.3.7b-*tetrahydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1) (XIX). 0·21 g IX nahmen in 15 cm³ Methanol in Gegenwart von Platin aus 30 mg PtO_2 in 4 Stdn. 0·97 Moläquival. Wasserstoff auf. Aus der eingeengten Lösung kristallisierten 0·17 g farbl. Nadeln (80%), die nach wiederholtem Umlösen aus Methanol bei 181–181·5° schmolzen.

($C_{14}H_{16}O_2$ (216·3) Ber.: C, 77·73; H, 7·45. Gef.: 77·46; H, 7·33.)

1a.5-*Dimethyl*-2.3-*dibrom*-1a.2.3.7b-*tetrahydro*-1H-*cyclopropa*[a]*naphthalin-carbonsäure*-(1) (XX). 0·38 g IX in 2 cm³ Chloroform wurden tropfenweise mit 20-proz. Bromlösung in Chloroform versetzt. Nach kurzem Stehen schieden sich 0·63 g blassgelbe Nadeln mit Schmp. 143–144° aus, die nach Umlösen aus Äther/Petroläther farblos waren; Ausb. 95%.

($C_{14}H_{14}Br_2O_2$ (374·1) Ber.: C, 44·95; H, 3·77; Br, 41·83. Gef.: C, 45·32; H, 3·73; Br, 42·73.)

1-[2'-*Carboxy*-4'-*methyl*]-2-*methyl*-*cyclopropan*-*dicarbonsäure*-(2.3) (XXI). 1·02 g IX wurden in 30 cm³ Essigester, wie für XV beschrieben, ozonisiert. Im Anschluss an die Zugabe von 1·65 g Natriumcarbonat in 15 cm³ Wasser und die Entfernung des Essigesters wurde mit 3 cm³ 30-proz. Wasserstoffperoxyd versetzt und 3 Stdn. auf 90° erwärmt. Der mit Säure ausgefällte Niederschlag wurde getrocknet und mit Benzol aufgekocht, wobei 0·22 g mit Schmp. 238–244° (17%) ungelöst blieben. Aus Essigester farbl. Polyeder mit Schmp. 246–247°.

($C_{14}H_{14}O_6$ (278·3) Ber.: C, 60·43; H, 5·07. Säureäquival. 92·8. Gef.: C, 60·89; H, 5·13. Säureäquival. 93·0.)

2.6-*Dimethyl*-*naphthyl*-(1)-*essigsäure* (XXII). Die Aromatisierung der Säure IX vollzog sich, wie bei VII beschrieben, mit Acetanhydrid/Schwefelsäure und lieferte 68% XXII: Aus Äthanol/Wasser farbl. Nadeln mit Schmp. 172–173°.

($C_{14}H_{14}O_2$ (214·3) Ber.: C, 78·48; H, 6·78; Säureäquival. 214. Gef. C, 78·75; H, 6·94. Säureäquival. 214.)

Der *Äthylester* kam aus Petroläther in farbl. Nadeln mit Schmp. 74–75°.

($C_{16}H_{18}O_2$ (242·3) Ber.: C, 79·31; H, 7·49. Gef.: C, 79·63; H, 7·49.)

Zur *unabhängigen Synthese* wurden 17 g 2.6-Dimethylnaphthalin mit 4·5 g Paraformaldehyd, 12 cm³ Eisessig, 14 cm³ konz. HCl und 7 g sirupös. Phosphorsäure 5 Stdn. rückflussgekocht. Nach Eingiessen in Wasser wurde das rohe Chlormethylierungsprodukt mit Kaliumcyanid in siedendem Alkohol umgesetzt. Die Hydrolyse des Nitrils mit 24-proz. Kalilauge gab 47% einer Rohsäure mit Schmp. 152–156°. Häufiges Umlösen aus Äthanol/Wasser steigerte den Schmp. auf 163–166°. Das Präparat gab mit XXII keine Erniedrigung im Misch-schmp., war aber noch nicht rein. Möglicherweise ist die Chlormethylierung nicht ausreichend auf die Position 1 beschränkt.

Isomerisierung zu 2.7-*Dimethyl*-5H-*benzocyclohepten*-*carbonsäure*-(6)-*äthylester* (X). 0·63 g Äthylester VIII wurden 5 Stdn. auf 250° erhitzt. Anschliessend gingen bei 125–128° (Badtemp.)/0·01 Torr 0·49 g blassgelben Öls über, das im IR-Spektrum völlig mit X übereinstimmte und zu XI hydrolysiert werden konnte.

2.7-*Dimethyl*-5H-*benzocyclohepten*-*carbonsäure*-(6) (XI) *Äthylester* X: Blassgelbes Öl mit $Sdp._{0·01}$ 122–123°.

2.7-*Dimethyl*-6.7.8.9-*tetrahydro*-*benzocyclohepten*-*carbonsäure*-(6) (XXIII). Die Säure XI nahm in Methanol in Gegenwart von Platin innerhalb 30 Min. 2·1 Moläquival. Wasserstoff auf. Aus Methanol/Wasser kristallisierten farbl. Nadeln mit Schmp. 106–107°. I.R.-Spektrum (KBr): Die CO-Schwingung bei 1686/cm entspricht einer nichtkonjugierten Carboxylgruppe. Die starke Bande bei 820/cm geht auf die CH-Waggingschwingung des 1.2.4-trisubst. Benzols zurück.

($C_{14}H_{18}O_2$ (218·3) Ber.: C, 77·10; H, 8·31. Gef.: C, 76·67; H, 8·15.)

Oxydation mit Kaliumpermanganat. 0·32 g XI wurden in 10 cm³ siedendem stabilem Aceton mit $KMnO_4$ behandelt, bis das Oxydans nicht mehr verbraucht wurde. Dann reduzierten wir mit schwefliger Säure, entfernten das Aceton und perforierten 20 Stdn. mit Äther. Die sich abscheidenden farbl. Kristalle zeigten Zers.-P. 209–210° und erwiesen sich als *Trimellitsäure*; der mit Diazomethan bereitete, bei 192–193°/12 Torr übergehende *Trimethylester* wurde identifiziert.

1a.4-*Dimethyl*-1a.1b.2a.6b-*tetrahydro-bis*-1.2H-*cyclopropa*[a,c]*naphthalin-dicarbonsäure*-(1.2) (XXV)

5·1 g *Esterfraktion B* (S. 13) wurden mit 30 cm³ 10-proz. methanolischer KOH verseift. Beim Aufkochen der trockenen Rohsäure mit Benzol blieben 3·1 g gelbbraune Kristalle vom Schmp. 221–229° ungelöst. Wiederholtes Umlösen aus Äthanol/Wasser und Methanol/Benzol führte zu farbl. mikrokristallinem Pulver mit Schmp. 250–251°.

($C_{16}H_{16}O_4$ (272·3) Ber.: C, 70·57; H, 5·92. Säureäquival. 136. Gef.: C, 69·34; H, 6·09. Säureäquival. 138.)

Die gleiche Dicarbonsäure XXV erhielten wir auch bei der thermischen oder kupferkatalysierten Umsetzung des *Äthylesters* VI mit Diazoessigester und nachfolgender Verseifung des im Hochvak. destillierten Produkts.

1-*Methyl-bicyclopropyl-tetracarbonsäure*-(2.3.2′.3′) (XXVI). 2·0 g XXV wurden mit Diazomethan in den *Dimethylester* übergeführt und in 40 cm³ Essigester 15 Stdn. bei Raumtemp. mit einem 4-proz. Ozonstrom behandelt. Nach Zugabe von 15 cm³ Wasser und 2 cm³ 30-proz. H_2O_2 wurde der Essigester entfernt; die zunächst trübe Lösung war nach 24 Stdn. klar. Mit NaOH wurde kräftig alkalisch gemacht und mit Äther perforiert. Nach Ansäuren mit Schwefelsäure erlaubte die 24-stdge. Ätherperforation die Isolierung von 0·35 g farbl. Kristallkrusten, die nach Umlösen aus Äther Zers.-P. 291–292° zeigten. Die U.V.-Absorption besitzt ein Maximum bei 216 mμ ($\log \varepsilon = 3{\cdot}0$) und einen langsamen Abfall nach dem Langwelligen mit Sätteln bei 271 und 297 mμ ($\log \varepsilon = 1{\cdot}90$ und $1{\cdot}75$). Das Spektrum der methylfreien Tetracarbonsäure[8] ist sehr ähnlich.

($C_{11}H_{12}O_8$ (272·2) Ber.: C, 48·54; H, 4·45. Säureäquival. 68. Gef.: C, 48·89; H, 4·35. Säureäquival. 66.)

Konkurrenzversuch Naphthalin/2.6-Dimethylnaphthalin

Die Mischung von je 0·25 Mol der beiden Kohlenwasserstoffe wurde bei 140° mit 10·0 g Diazoessigsäure-äthylester wie S. 13 umgesetzt. Nach Abtrennung der überschüssigen Kohlenwasserstoffe durch Kristallisation aus Methanol wurde das bei 99–135°/0·05 Torr übergehende Estergemisch I.R.-analysiert. Die Extinktion der Bande des Rohesters A (S. 13) bei 805/cm wurde als Mass für den Angriff des Carbäthoxycarbens auf 2.6-Dimethylnaphthalin gewählt, während die Banden bei 747, 775 und 980/cm für den Rohester aus Naphthalin und Diazossigester typisch erschienen. In 112 mg Mischester wurden so 70 und 23 mg der Konkurrenzprodukte nachgewiesen. Das Molverhältnis, in dem 2.6-Dimethyl-naphthalin und Naphthalin angegriffen wurden, beträgt somit 10:3·6.

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SYNTHESIS OF *TRANS*-10-HYDROXYDEC-2-ENOIC ACID* AND RELATED COMPOUNDS

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Abstract—Syntheses of the two stereoisomeric 10-hydroxydec-2-enoic acids are described. The *trans*-isomer is identical with the main fatty acid isolated from royal jelly of honeybees.

Some compounds closely related to this *trans*-acid have also been prepared.

A convenient process for the preparation of 10-acetoxy-decanoic acid from castor oil has been developed.

The lipid portion of royal jelly of honeybees has as chief constituent a C_{10}-fatty acid, which was first isolated by Townsend and Lucas[1] and later characterized as 10-hydroxydec-2-enoic acid by Butenandt and Rembold.[2] A recent observation[3] that this acid can under special conditions completely suppress the development of transplantable leukaemia and ascitic tumours in mice prompted us to synthesize it and analogous bifunctional compounds for comparative biological studies.

At that stage the configuration of the olefinic linkage in this unsaturated hydroxy-acid was still undetermined; it was apparently not possible to draw any definite conclusions from the infra-red spectrum.[4] We therefore decided to synthesize both stereoisomerides of 10-hydroxydec-2-enoic acid. Brief accounts of these syntheses have been published elsewhere[5,6] and they have been patented.[7,8]

As has already been recorded,[5,7] synthetic *trans*-10-hydroxydec-2-enoic acid (I, R = H), m.p. 64–65° proved to be identical with the acid from natural sources, for which m.p. 54–56° had been quoted.[2] We are most grateful to Dr. H. Rembold of the Max-Planck Institut für Biochemie, München and to Dr. W. H. Brown of the Ontario Agricultural College, Guelph, Canada, for providing samples of the natural acid, which enabled us to identify the compound by the mixed melting point and a comparison of the infra-red spectra. Shortly after our patent application concerning the *trans*-acid[7] had been filed, nuclear magnetic resonance data were published[9] which confirmed that the natural product was the *trans*-isomer.

We prepared royal jelly acid (I, R = H) by two methods frequently used for synthesizing α,β-unsaturated *trans*-acids. In our case this involved (a) elimination of hydrogen iodide from 10-acetoxy-2-iododecanoic acid (II) or its methyl ester (III) by means of

* We propose the term royal jelly acid for this compound.

[1] G. F. Townsend and C. C. Lucas, *Biochem. J.* **34**, 1155 (1940).
[2] A. Butenandt and H. Rembold, *Z. Physiol. Chem.* **308**, 284 (1957).
[3] G. F. Townsend, J. F. Morgan and B. Hazlett, *Nature, Lond.* **183**, 1270 (1959).
[4] S. A. Barker, A. B. Foster and D. C. Lamb, *Nature, Lond.* **183**, 996 (1959).
[5] G. I. Fray, R. H. Jaeger and Sir Robert Robinson, *Tetrahedron Letters* No. 4, 15 (1960).
[6] G. I. Fray, E. D. Morgan and Sir Robert Robinson, *Tetrahedron Letters* No. 13, 34 (1960).
[7] U. K. Patent Application No. 25692/59 (27.7.1959).
[8] U. K. Patent Application No. 8576/60 (1960).
[9] S. A. Barker, A. B. Foster and D. C. Lamb, *Nature, Lond.* **184**, 634 (1959).

alkali, and (b) condensation of 8-acetoxyoctanal (IV) with malonic acid under the conditions of the Doebner reaction, followed by hydrolysis of the acetyl group. Since our earlier publication[5] we have considerably improved these two processes and we are confining ourselves in the present communication to a description of the reaction conditions which gave us the best results.

$HO\cdot(CH_2)_7\cdot CH\overset{t}{=}CH\cdot CO_2R$
I

$CH_3COO\cdot(CH_2)_7\cdot CHO$
IV

$CH_3COO\cdot(CH_2)_8\cdot CHX\ COR$
II (X = I; R = OH)
III (X = I; R = OMe)
V (X = Br; R = Cl)
VI (X = Br; R = OH)
VII (X = Br; R = OMe or OBu^t)

10-Acetoxydecanoic acid can now be very conveniently prepared from castor oil by our modification[10] of a patented process.[11] This acid was converted by means of thionyl chloride into the acid chloride, which was brominated without previous isolation, and the resulting product was hydrolysed with water to the crude bromo-acid (VI). After reaction of this with sodium iodide in methyl ethyl ketone[12] and treatment of the resulting iodo-acid (II) with alcoholic potassium hydroxide *trans*-10-hydroxydec-2-enoic acid (I, R = H), m.p. 64–65° was isolated by one crystallization from ether–light petroleum (b.p. 40–60°).

Alternately, the crude brominated acid chloride (V) was converted into the corresponding bromo-esters (VII) by reaction with the appropriate alcohol in pyridine; the presence of pyridine is essential to prevent transesterification and the resulting formation of polyesters. Attempts to dehydrobrominate the ester (VII; R = OBu^t) with diethylaniline[13] were unsuccessful, whereas conversion of the ester (VII; R = OMe) into the iodo-ester (III) with sodium iodide in acetone, followed by treatment with methanolic potassium hydroxide, was satisfactory.

The preferred method for preparing 8-acetoxyoctanal (IV), which was required as an intermediate for the second route to royal jelly acid (I; R = H), consisted in converting 8-bromo-octanoic acid[14] into 8-acetoxyoctanoic acid; from this the aldehyde (IV) was obtained by Rosenmund reduction of the acid chloride.

We also prepared the aldehyde (IV)—though in very poor yield—from 8-acetoxy-1-bromo-octane[15] via the tosylate (VIII; Ts = toluene-*p*-sulphonyl) which was oxidized by means of dimethyl sulphoxide in the presence of sodium hydrogen carbonate.[16]

$CH_3COO\cdot(CH_2)_8\cdot OTs$
VIII

Doebner condensation of 8-acetoxyoctanal (IV) with malonic acid, followed by hydrolysis of the resulting *trans*-10-acetoxydec-2-enoic acid yielded very pure royal jelly acid (I, R = H). The methyl ester (I, R = Me) was prepared from the parent acid with diazomethane.

An attempt to apply the Wittig reaction to the synthesis of the acid (I, R = H)

[10] U. K. Patent Application No. 30163/60 (1960).
[11] U. K. Patent No. 675434 (1952).
[12] R. S. Sweet and F. I. Estes, *J. Org. Chem.* **21**, 1426 (1956).
[13] G. D. Hunter and G. Popják, *Biochem. J.* **50**, 163 (1951).
[14] F. Salmon-Legagneur and C. Neveu, *Bull. Soc. Chim. Fr.* 1345 (1956).
[15] F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider and J. F. Walker, *J. Org. Chem.* **21**, 739 (1956).
[16] N. Kornblum, W. J. Jones and G. J. Anderson, *J. Amer. Chem. Soc.* **81**, 4113 (1959).

from acetoxyoctanal (IV), using methoxycarbonylmethylenetriphenylphosphorane,[17] produced the desired substance only in low yield.

The chosen route to *cis*-10-hydroxydec-2-enoic acid (IX)[6,8] was by way of the acetylenic acid (X), since the partial hydrogenation of such acids in the presence of Lindlar's catalyst[18] is known to give the corresponding *cis*-ethylenic compounds with a high degree of stereospecificity.

$HO\cdot(CH_2)_7\cdot CH{=}CH\cdot CO_2H$ (c)
IX

$HO\cdot(CH_2)_7\cdot C{\equiv}C\cdot CO_2H$
X

$Py\cdot O\cdot(CH_2)_7\cdot X$
XI

$Py\cdot O\cdot(CH_2)_7\cdot C{\equiv}CH$
XII

XI-XIII (Py = 2-Tetrahydropyranyl)

$[Py\cdot O\cdot(CH_2)_7\cdot C{\equiv}C]_2\,Mg$
XIII

7-Chloroheptanol[19] was converted into the corresponding tetrahydropyranyl ether (XI, X = Cl) from which the crude iodo-compound (XI, X = I) was obtained by halogen exchange in the known manner. Reaction of the iodide with sodium acetylide in dimethylformamide according to a method recommended for the preparation of long-chain alk-1-ynes[20] yielded tetrahydropyranyloxynon-1-yne (XII). Since it has been demonstrated that magnesium acetylides can be very readily carboxylated,[21] the acetylenic compound (XII) was converted by means of diethyl magnesium into the magnesium derivative (XIII), which was treated with solid carbon dioxide. The resulting crude acid was immediately hydrolysed to 10-hydroxydec-2-ynoic acid (X), m.p. 72–73°; reduction with Lindlar's catalyst [18] gave *cis*-10-hydroxydec-2-enoic acid (IX), m.p. 73·5–74·5° in virtually quantitative yield.

Our next objective was the synthesis of some compounds structurally related to royal jelly acid, in order to examine whether such analogues also possessed cancer-inhibiting properties. In this connection the C_{12}-homologue (XIV, R = H) of royal jelly acid appeared to be particularly interesting since it also bears some relationship to traumatic acid (*trans*-dodec-2-en-1,12-dioic acid),[22] which is known to affect the cell growth of plants.

$RO\cdot(CH_2)_9\cdot CH{=}CH\cdot CO_2H$ (t)
XIV

trans-12-Hydroxydodec-2-enoic acid (XIV, R = H) was obtained by the Doebner reaction from malonic acid and 10-acetoxydecanal; this aldehyde was prepared from 10-acetoxydecanoic acid[10] by Rosenmund reduction of the derived acid chloride. Hydrolysis of the acetoxy-acid (XIV, R = CH_3CO) then furnished the C_{12}-hydroxy-acid (XIV, R = H).

The decision to synthesize the compound XV was influenced by the consideration that this substance may be regarded as an analogue of I (R = Me) in which an oxygen

[17] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helv. Chim. Acta* **40**, 1242 (1957).
[18] H. Lindlar, *Helv. Chim. Acta* **35**, 446 (1952).
[19] W. R. Coleman and W. G. Bywater, *J. Amer. Chem. Soc.* **66**, 1821 (1944).
[20] E. F. Jenny and K. D. Meier, *Angew. Chem.* **71**, 245 (1959).
[21] J. H. Wotiz, C. A. Hollingsworth and R. E. Dessy, *J Amer. Chem. Soc.* **78**, 1221 (1956).
[22] J. English Jr., J. Bonner and A. J. Haagen-Smit, *J. Amer. Chem. Soc.* **63**, 941 (1941).

atom replaces the C_8-methylene group; furthermore, the starting materials required for this synthesis were readily available.

$$HO{\cdot}(CH_2)_2{\cdot}O{\cdot}(CH_2)_4{\cdot}CH{=}CH{\cdot}CO_2Me$$
XV

Condensation of 5-hydroxypentanal[23] with malonic acid by Doebner's method gave a mixture consisting of tetrahydropyranylacetic acid[24] (XVI, R = H) and the desired *trans*-7-hydroxyhept-2-enoic acid (XVII, R = H), which could not be separated by distillation owing to the formation of polyesters. The crude mixture was therefore esterified and the two isomeric esters (XVI, R = Me) and (XVII, R = Me) isolated by fractionation; the latter was characterized as the solid 3,5-dinitrophenylurethan.

XVI

$$HO{\cdot}(CH_2)_4{\cdot}CH{=}CH{\cdot}CO_2R$$
XVII

Alkaline hydrolysis of the hydroxy-ester (XVII, R = Me) did not furnish the corresponding acid (XVII, R = H), but caused complete re-arrangement to tetrahydropyranylacetic acid[24] (XVI, R = H). The hydroxyethylation of the ester (XVII, R = Me) was achieved by converting it first into the tosylate (XVIII, Ts = toluene-*p*-sulphonyl), and treating this with the monosodio-derivative of ethylene glycol. Transesterification evidently took place during this process; the crude reaction product was therefore hydrolysed and re-esterified with methanol, yielding methyl *trans*-7-(2′-hydroxyethoxy)-hept-2-enoate (XV, R = Me), which formed a crystalline 3,5-dinitrophenylurethan.

$$TsO{\cdot}(CH_2)_4{\cdot}\overset{I}{C}H{=}CH{\cdot}CO_2Me$$
XVIII

The acidic product isolated after hydrolysis of the ester (XV, R = Me) failed to crystallize and could not be distilled, since this would have given rise to polyesters. We have, however, been informed[25] that methyl esters are now used in preference to the parent acids in the biological tests for which the compounds described in this paper have been prepared.

EXPERIMENTAL

Light petroleum without further definition means the fraction of b.p. 40–60°. Ethereal extracts were dried over magnesium sulphate. Infra-red spectra of solids were determined for Nujol mulls. Ultra-violet absorption data refer to ethanolic solutions.

Preparation of 10-*acetoxydecanoic acid from castor oil*

A mixture of sodium hydroxide (115 g), water (40 cc), tri-cresol (45 g) and castor oil (150 g) was heated under reflux at a bath temp of 180–195°, with vigorous stirring. The violent frothing occurring in the earlier stages of the reaction was kept under control by stirring at high speed. After 3 hr the volatile products were allowed to distil. The residue was cautiously dissolved in water (1·5 l.), acidified to Congo red with 50% sulphuric acid, and the mixture heated to boiling. The oily layer was separated while hot in a pre-heated separating funnel, diluted with ether and the solution was dried. After removal of the ether, the residue (ca. 175 g) was refluxed with acetic anhydride (350 cc) for 5–6 hr, the reaction mixture poured onto ice and left overnight. The product was collected in

[23] G. F. Woods, *Org. Synth.* Coll. Vol. III, 470 (1955).
[24] R. P. Zelinski, N. G. Peterson and H. R. Wallner, *J. Amer. Chem. Soc.* **74**, 1504 (1952).
[25] Professor G. F. Townsend, private communication.

ether, the ethereal extract thoroughly washed with water, and dried. After removal of the solvent, the residue was carefully fractionated. First a fraction of b.p. 136–160°/0·2 mm was collected; refractionation of this gave a fraction, b.p. 140–146°/0·2 mm and final fractionation yielded pure 10-acetoxydecanoic acid (45 g), b.p. 140–142°/0·2 mm. A sample had m.p. 36° (as quoted in the lit.[26]) after crystallization from light petroleum (b.p. below 30°).

By adopting the following procedure it was found possible considerably to reduce the volume to be fractionated without serious loss of the required material. Before acetylation, the oily layer of acidic products, isolated from the hot, aqueous mixture and dried as before, was dissolved in hot light petroleum (b.p. 60–80°; 300 cc), and the solution allowed to cool. The supernatant liquid was decanted from the precipitated material, which was then acetylated as described above to yield 10-acetoxydecanoic acid (41 g) from 150 g of castor oil.

(i) trans-10-*Hydroxydec*-2-*enoic acid* (I, R = H) *from* 10-*acetoxydecanoic acid*

(a) *Preparation* via 10-*acetoxy*-2-*bromodecanoic acid* (VI). 10-Acetoxydecanoic acid (23·6 g) was refluxed with purified thionyl chloride (30 cc) on the steam bath for 1½ hr. Bromine was then added slowly over a period of 2 hr to the refluxing solution and refluxing continued for a further 3 hr. The excess of the reagents was removed under reduced press and the residue poured into water (600cc). The mixture was warmed with shaking for 15 min (internal temp 40–50°) and finally kept at room temp overnight. The material was collected in ether, washed until the washings were neutral to litmus, and the extract rigorously dried. The crude bromo-acid (32 g) was refluxed with sodium iodide (33 g) and methyl ethyl ketone (330 cc) on the steam bath for 2 hr. After cooling, sodium bromide (11·5 g; 100%) was filtered off, the solid washed with dry acetone and the filtrate concentrated under reduced press. The residue was diluted with water, and acidified to Congo red with dilute sulphuric acid at 0°. The mixture was shaken with 10% aqueous sodium hydrogen sulphite, and the product collected with ether, washed and dried. The crude iodo-acid (36 g) was diluted with a little methanol and added in a thin stream to a hot solution of potassium hydroxide (30 g) in methanol (120 cc) under nitrogen. After refluxing for 3 hr, the mixture was concentrated *in vacuo*, and sufficient water was added to dissolve the precipitated salt. Some undissolved material was removed by means of ether, the aqueous portion acidified at 0° with 25% sulphuric acid, and the oily product collected with ether. The ethereal extract, after being washed with saline and dried, was decolourized with activated charcoal, filtered and concentrated to a small volume; light petroleum was added and, after several days in the refrigerator, trans-10-*hydroxydec*-2-*enoic acid* (4·98 g) was obtained as colourless prisms, m.p. 64·5–65°; a further amount (0·6 g), m.p. 64°, crystallized from the concentrated mother liquor (Found: C, 64·4; H, 9·6. $C_{10}H_{18}O_3$ requires: C, 64·5; H, 9·7%). Ultra-violet absorption: max 211 mμ (ε 12000). The infra-red spectrum had bands at 2·92 (free OH), 5·89 (conjugated C=O) and 6·05 (conjugated C=C) μ; the band at 10·17 μ cannot be quoted as characteristic for the *trans*-ethylenic linkage since both 10-hydroxydecanoic acid[4] and *cis*-10-hydroxydec-2-enoic acid absorb in this region. The acid proved to be identical with 10-hydroxydec-2-enoic acid from natural sources (mixed m.p. and infra-red spectra).

(b) *Preparation* via *methyl* 10-*acetoxy*-2-*bromodecanoate* (VII, R = OMe). 10-Acetoxydecanoic acid (49 g) was converted as before into the crude bromo-acid chloride, which was poured slowly into an ice-cold mixture of dry methanol (50 cc) and dry pyridine (25 cc) and left for 4 hr. The product was isolated by adding ether and washing successively with dil sulphuric acid, water, and dil sodium hydroxide. The ethereal solution was dried, the solvent evaporated and the residue fractionated to give *methyl* 10-*acetoxy*-2-*bromodecanoate* (56·6 g), b.p. 130–134°/0·2 mm (Found: C, 48·4; H, 7·3. $C_{13}H_{23}O_4Br$ requires: C, 48·3; H, 7·2%). The bromo-ester (19 g) was refluxed with sodium iodide (19 g) in acetone (150 cc) for 1 hr, the mixture was then concentrated, and ether and water added to the remainder; the ether layer was washed with sodium thiosulphate solution, dried and evaporated. The crude iodo-ester was refluxed with a solution of potassium hydroxide (40 g) in methanol (140 cc) for 2½ hr, diluted with water, acidified and extracted with ether. The extract was washed with saturated aqueous sodium chloride, dried and evaporated. Crystallization of the oily residue from ether–light petroleum in the refrigerator yielded *trans*-10-hydroxydec-2-enoic acid (4·75 g), m.p. 62–64°. Chromatography of the mother liquor gave more material (0·5 g) of the same m.p.

Isobutyl 10-*acetoxy*-2-*bromodecanoate* (VII, R = OBu^i). This was prepared from 10-acetoxydecanoic acid (23 g) in the same manner as the corresponding methyl ester, using isobutanol (20 cc)

[26] P. Chuit, *Helv. Chim. Acta* **9**, 1074 (1926).

and pyridine (12 cc); fractionation yielded the *ester* (29·5 g), b.p. 140–142°/0·1 mm (Found: C, 52·3; H, 8·3. $C_{16}H_{29}O_4Br$ requires: C, 52·6; H, 8·0%). Refluxing this bromo-ester with diethylaniline[18] and hydrolysing the reaction product failed to produce *trans*-10-hydroxydec-2-enoic acid.

8-*Acetoxyoctanal* (IV). 8-Bromo-octanoic acid[14] (33 g) was refluxed with silver acetate (27 g) and glacial acetic acid (270 cc) for 3 hr. The resulting 8-acetoxyoctanoic acid[27] (28 g) was heated on the steam bath with purified thionyl chloride (15 cc) and dry benzene (50 cc) for 1 hr; excess reagent and solvent were removed under reduced press and the residue distilled, to give the acid chloride as a colourless liquid (27 g), b.p. 94–96°/0·2 mm. The acid chloride (26 g), dry xylene (200 cc) and 5% palladized barium sulphate (3·4 g) were heated in an oil bath at 150–160° while a vigorous stream of hydrogen was passed through the stirred mixture. After 45 min the evolution of hydrogen chloride slowed down appreciably, and the reaction was stopped after a further 15 min. The mixture was chilled, some Celite added to it, and the solids removed by filtration. After concentration of the filtrate under reduced press on the steam bath, the residue was fractionated; 8-*acetoxyoctanal* was obtained as a colourless, fragrant liquid (16 g), b.p. 80–82°/0·3 mm (Found: C, 64·3; H, 9·7. $C_{10}H_{18}O_3$ requires: C, 64·5; H, 9·7%). Its infra-red spectrum had bands at 3·67 (aldehydic C—H) and 5·75 μ (C=O).

The 2,4-*dinitrophenylhydrazone* was prepared in pyridine according to Braude's method,[28] and crystallized from benzene–light petroleum (b.p. 60–80°) as fine, yellow needles, m.p. 75° (Found: C, 52·7; H, 6·0; N, 15·5. $C_{16}H_{22}O_6N_4$ requires: C, 52·5; H, 6·0; N, 15·3%).

A small quantity of the above aldehyde was also obtained when 8-acetoxy-1-toluene-*p*-sulphonyloxyoctane (VIII; 24 g)—prepared from 8-acetoxy-1-bromo-octane[15] (27 g) by reaction with silver toluene-*p*-sulphonate (39 g) in acetonitrile (250 cc)—was treated with dimethyl sulphoxide (450 cc) and sodium hydrogen carbonate (60 g) according to the procedure of Kornblum *et al.*[16] The aldehyde (2·4 g) was isolated by means of its bisulphite addition compound.

(ii) trans-10-*Hydroxydec*-2-*enoic acid* (I; R = H) *from* 8-*acetoxyoctanal*

(a) *By the Doebner reaction.* 8-Acetoxyoctanal (8·7 g) and malonic acid (5·2 g), each dissolved in pyridine (20 cc), were mixed at 0° and piperidine (15 drops) was added. The solution was kept at 50° for 48 hr, with exclusion of moisture and light. The reaction mixture was then chilled in ice, acidified with ice-cold 50% sulphuric acid (80 cc), and the product collected in ether. The ethereal layer was shaken with dilute hydrochloric acid, dried and evaporated. Fractionation of the residue gave trans-10-*acetoxydec*-2-*enoic acid* as a colourless oil (7·8 g), b.p. 148–151°/0·2 mm (Found: C, 62·9; H, 8·9. $C_{12}H_{20}O_4$ requires: C, 63·1; H, 8·8%); its infra-red spectrum had bands at 5·78 (C=O), 5·9 (conjugated C=O) and 6·07 μ (conjugated C=C). The acetoxy-acid (7·5 g) was refluxed under nitrogen for 3 hr, with potassium hydroxide (5 g), water (10 cc) and ethanol (50 cc). Most of the alcohol was removed under reduced press, the residue diluted with a little water, and the alkaline solution extracted with ether to remove some impurity. The aqueous layer was acidified at 0° with 25% sulphuric acid, saturated with ammonium sulphate, and extracted with ether. The extract was washed with a little water, dried and evaporated, leaving a residue (5·6 g), which solidified on trituration with light petroleum and crystallized from ether–light petroleum as rosettes of colourless prisms (4 g), m.p. 63°; a second crystallization from the same solvent mixture raised the m.p. to 64–65°. This material was identical with *trans*-10-hydroxydec-2-enoic acid prepared from 10-acetoxydecanoic acid.

(b) *By the Wittig reaction.* Reaction of a solution of 8-acetoxyoctanal (2·3 g) in benzene (80 cc) with methoxycarbonylmethylenetriphenylphosphorane (4·1 g) under the conditions described by Isler *et al.*[17] yielded *methyl* trans-10-*acetoxydec*-2-*enoate* (2·0 g), b.p. 133–135°/0·5 mm (Found: C, 64·5; H, 9·3. $C_{13}H_{22}O_4$ requires: C, 64·4; H, 9·1%). Hydrolysis of this ester (2·0 g) with methanolic potassium hydroxide gave an oil (1·4 g), which failed to crystallize. After chromatographic separation on Florex, the *trans*-acid (0·19 g), m.p. 64·5–65°, identical with previously prepared specimens, was obtained.

Methyl trans-10-*hydroxydec*-2-*enoate* (I, R = Me). A solution of the acid (I, R = H; 5 g) in ether (50 cc) was treated with an ethereal solution of diazomethane. After removal of the solvent the residue was distilled to give the *ester* (5 g) as a colourless liquid, b.p. 115–118°/0·15 mm, n_D^{22} 1·4660 (Found: C, 67·9; H, 10·5. $C_{13}H_{24}O_3$ requires: C, 68·4; H, 10·5%).

[27] P. Chuit, *Helv. Chim. Acta* **12**, 465 (1929).
[28] E. A. Braude, *J. Chem. Soc.* 3131 (1953).

Synthesis of cis-10-*hydroxydec-2-enoic acid* (IX)

7-*Chloro*-1-2′-*tetrahydropyranyloxyheptane* (XI; X = Cl). Two drops of conc hydrochloric acid were added to 7-chloroheptanol[19] (38 g) in 2,3-dihydropyran (25 g) at 0°. Distillation from a few pellets of potassium hydroxide gave 7-*chloro*-1-2′-*tetrahydropyranyloxyheptane* (53 g), b.p. 92–95°/0·2 mm, n_D^{25} 1·4605 (Found: Cl, 14·9. $C_{12}H_{23}O_2Cl$ requires: Cl, 15·1%).

9-2′-*Tetrahydropyranyloxynon*-1-*yne* (XII). The above ether (13·5 g) was refluxed with sodium iodide (18 g) in acetone (150 cc) for 5 hr. The precipitated sodium chloride was removed and the filtrate refluxed with a further quantity of sodium iodide (2 g) for 7 hr. The reaction mixture was filtered, and the filtrate was diluted with ether, washed with sodium thiosulphate solution and water, and dried. After evaporation of the solvent, the crude iodide (XI; X = I; 18 g) was dissolved in dimethylformamide (150 cc) and slowly added to sodium acetylide (from 5·3 g of sodium) in liquid ammonia (500 cc). The ammonia was allowed to evaporate, and the remaining solution was stirred at 70° under nitrogen for 4 hr, cooled in ice and extracted with ether. The extract was washed successively with dil hydrochloric acid, aqueous sodium hydroxide and water, and was then dried and freed from the solvent; fractionation afforded 9-2′-*tetrahydropyranyloxynon*-1-*yne* (8·25 g), b.p. 90–91°/0·3 mm, n_D^{25} 1·4518 (Found: C, 75·1; H, 10·7. $C_{14}H_{24}O_2$ requires: C, 75·0; H, 10·8%). The infra-red spectrum exhibited bands at 3·05 (C≡CH) and 4·75 μ (C≡C).

10-*Hydroxydec*-2-*ynoic acid* (X). Ethylmagnesium bromide, prepared from ethyl bromide (5·25 g) and magnesium (0·8 g) in ether (60 cc) was refluxed for 5 hr with dioxan (2·9 g, purified by treatment with ethylmagnesium bromide in ether, followed by distillation). Tetrahydropyranyloxynon-1-yne (6·7 g) in ether (20 cc) was added, and the mixture refluxed, with stirring, for 1 hr. The product was poured onto solid carbon dioxide, left for 1 hr, and then shaken with saturated ammonium chloride solution to which a few drops of dil hydrochloric acid had been added. The ethereal solution was extracted with aqueous sodium carbonate, and the extracts acidified. Collection of the product with ether yielded crude 10-2′-tetrahydropyranyloxydec-2-ynoic acid (4·6 g), which was refluxed with methanol (30 cc) and water (30 cc) containing a little toluene-*p*-sulphonic acid. Removal of the solvent and crystallization from ether–light petroleum (b.p. 60–80°) furnished 10-*hydroxydec*-2-*ynoic* acid (2·1 g), m.p. 72–73° (Found: C, 65·4; H, 8·7. $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·8%). The infra-red spectrum had bands at 3·06 (free OH), 4·45 (C≡C) and 6·02 μ (C=O).

cis-10-*Hydroxydec*-2-*enoic acid* (IX). The above acetylenic acid (1·52 g) was hydrogenated in ethyl acetate (50 cc) in the presence of Lindlar's catalyst[18] (0·4 g) and quinoline (1 drop) until one equivalent of hydrogen had been absorbed. After removal of the catalyst by filtration and evaporation of the solvent, the residue crystallized from ether–light petroleum (b.p. 60–80°), yielding cis-10-*hydroxydec*-2-*enoic acid* (1·35 g) as colourless prisms, m.p. 73·5–74·5° (Found: C, 64·4; H, 9·6. $C_{10}H_{18}O_3$ requires: C, 64·5; H, 9·7%). The ultra-violet absorption showed a maximum at 210 mμ (ε 12,450). The infra-red spectrum had bands at 2·90 (free OH), 5·92 (conjugated C=O), 6·15 (conjugated C=C) and 12·3 μ (*cis* CH=CH).

Synthesis of compounds related to royal jelly acid

10-*Acetoxydecanal*. 10-Acetoxydecanoic acid (10·1 g) was converted into the acid chloride (10·7 g), b.p. 108°/0·15 mm, which was reduced with hydrogen in the presence of 5% palladized barium sulphate, as described for the preparation of 8-acetoxyoctanal; fractionation yielded 10-*acetoxydecanal* (6·7 g), b.p. 110°/0·4 mm (Found: C, 66·8; H, 10·2. $C_{12}H_{22}O_3$ requires: C, 67·3; H, 10·3%). The infra-red spectrum had bands at 3·70 (aldehydic C—H) and 5·75 μ (C=O).

trans-12-*Acetoxydodec*-2-*enoic acid* (XIV, R = CH_3CO). A solution of malonic acid (3·5 g) in dry pyridine (20 cc) was added at 0° to 10-acetoxydecanal (6·3 g), followed by piperidine (0·6 cc). The mixture was kept at room temp overnight and then warmed under nitrogen at 50–55° for 1 hr and at 90° for 3 hr. The reaction mixture was worked up as described for the preparation of *trans*-10-hydroxydec-2-enoic acid by the Doebner reaction. trans-12-*Acetoxydodec*-2-*enoic acid* separated from light petroleum (b.p. 60–80°) as yellowish prisms (4·2 g), m.p. 42·5–43° (Found: C, 65·4; H, 9·0. $C_{14}H_{24}O_4$ requires: C, 65·6; H, 9·4%). Its infra-red spectrum had bands at 5·76 (C=O), 5·90 (conjugated C=O) and 6·06 μ (conjugated C=C).

trans-12-*Hydroxydodec*-2-*enoic acid* (XIV, R = H). The above acetoxyacid (3·2 g) was refluxed with a solution of potassium hydroxide (2 g) in water (5 cc) and ethanol (20 cc) for 3 hr under nitrogen. The solution was concentrated *in vacuo*, water was added and the acid precipitated at 0° with 25% sulphuric acid. The solid was washed with water, dissolved in ether and the ethereal solution shaken

with conc brine, and dried. trans-12-*Hydroxydodec-2-enoic acid* (2·5 g) crystallized from ether, m.p. 69–69·5°; a second crystallization from ether–light petroleum raised the m.p. to 70–71° (Found: C, 67·7; H, 10·3. $C_{12}H_{22}O_3$ requires: C, 67·4; H, 10·3%). The infra-red spectrum showed bands at 2·96 (free OH), 5·92 (conjugated C=O) and 6·07 μ (conjugated C=C).

Methyl trans-7-*hydroxyhept-2-enoate* (XVII, R = Me). 5-Hydroxypentanal[23] (50 g) was added to a cold solution of malonic acid (104 g) in pyridine (160 cc) containing piperidine (5 cc); the mixture was kept at room temp for 5 days, and then finally heated on the steam bath for 5 hr. The solvent was removed under reduced press, the oily residue (81 g) mixed with methanol (2l) and conc sulphuric acid (25 cc), and the mixture left at room temp. for 9 days. The resulting solution was concentrated under reduced press, and added to a mixture of ether and ice. The ethereal solution was washed with aqueous sodium hydrogen carbonate and water, dried and evaporated; fractionation gave methyl tetrahydropyran-2-ylacetate (XVI, R = Me; 14·6 g), b.p. 106–110°/26 mm, followed by *methyl* trans-7-*hydroxyhept-2-enoate* (32 g), b.p. 110–113°/0·4 mm, n_D^{20} 1·4675 (Found: C, 60·7; H, 9·0. $C_8H_{14}O_3$ requires: C, 60·7; H, 8·9%). The infra-red spectrum had bands at 2·95 (free OH), 5·82 (conjugated C=O) and 6·05 μ (conjugated C=C). The 3,5-*dinitrophenylurethan* crystallized from methanol, m.p. 124–125·5° (Found: C, 48·5; H, 4·9; N, 11·7. $C_{15}H_{17}N_3O_8$ requires: C, 49·0; H, 4·7; N, 11·4%).

Alkaline hydrolysis of methyl *trans*-7-hydroxyhept-2-enoate (2·1 g) afforded tetrahydropyran-2-ylacetic acid (1·8 g), m.p. 56–58°,[24] after crystallization from ether–light petroleum, as the sole product of the reaction.

Methyl trans-7-(2′-*hydroxyethoxy*)-*hept*-2-*enoate* (XV). Pyridine (16 cc) was added to a stirred mixture of methyl *trans*-7-hydroxyhept-2-enoate (7·9 g) and toluene-*p*-sulphonyl chloride (10·5 g) cooled in ice–salt, at such a rate that the temperature did not exceed 0°. After the addition (1 hr), stirring was continued for 3 hr, while the temp was allowed to rise gradually to 15°. A mixture of conc hydrochloric acid (50 cc) and crushed ice (100 g) was added, and the product was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The resulting crude toluene-*p*-sulphonate (13·9 g) was added to a solution of sodium (1·06 g) in ethylene glycol (18 cc), and the mixture stirred under nitrogen at 60–65° (bath) for 4 hr, then at 80–90° (bath) for 45 min, and was finally left overnight at room temp. Water (25 cc) was added and the solution extracted continuously with ether for 12 hr. Evaporation of the ether gave an oil (6·2 g), which was heated on the steam bath for 4 hr with a solution of sodium hydroxide (2·5 g) in water (4 cc). After acidification and collection with ether, the product (3·2 g) was refluxed with methanol (80 cc) and conc sulphuric acid (0·7 cc) for 12 hr. Working up in the usual way yielded, after fractional distillation, *methyl* trans-7-(2′-*hydroxyethoxy*)-*hept*-2-*enoate* (1·2 g), b.p. 104–106°/0·08 mm, n_D^{20} 1·4623 (Found: C, 59·6; H, 9·0. $C_{10}H_{18}O_4$ requires: C, 59·4; H, 9·0%). The infra-red spectrum had bands at 2·92 (free OH), 5·80 (conjugated C=O), 6·04 (conjugated C=C) and 8·91 μ (ether C—O). The 3,5-*dinitrophenylurethan* crystallized from methanol, m.p. 110–111·5° (Found: C, 49·8; H, 5·1; N, 10·5. $C_{17}H_{21}N_3O_9$ requires: C, 49·6; H, 5·1; N, 10·2%).

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NEW HETEROAROMATIC COMPOUNDS—XII[1]

FURTHER EVIDENCE FOR THE AROMATICITY OF THE BORAZARENES

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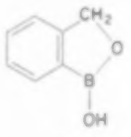
Abstract—Snyder and his co-workers[2] have reported that the cyclic boric ester (I) is stable to hydrolysis and may be nitrated. These observations suggests that the stability of the heterocyclic boron compounds described in previous papers of this series might be due to their cyclic nature rather than to aromatic resonance. Their reactions with bases, and a comparison of the properties of 2:1-borazaronaphthalenes with those of their 3:4-dihydro derivatives seem to make this unlikely.

SNYDER[2] has reported that the internal ester (I) of *o*-hydroxymethyl phenylboronic acid is resistant to hydrolysis and may be nitrated; this suggests that part or even all of the stability of the heterocyclic boron compounds described in earlier papers of series might be due to their cyclic structures rather than to aromaticity of the boron-containing rings. Here we present additional evidence suggesting that this is not the case and that our compounds owe their stability to their aromatic structure. Part of this new evidence refers to the reactions of borazarene derivatives with bases and part to a comparison of the properties of derivatives of 2:1-borazaronaphthalene with those of the corresponding non-aromatic 3:4-dihydro derivatives.

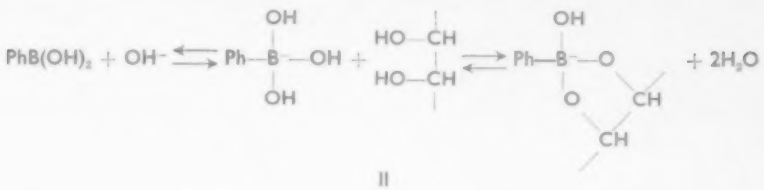


I

The acidity of a compound containing a hydroxy-substituted boron atom may arise in two ways. The acid may lose a proton to give a trigonal planar anion, or the boron atom may behave as a Lewis acid centre, and coordinate with a hydroxyl anion. The configuration about the boron atom would then be tetrahedral. The latter structure has been favored for the borate ion, on the basis of Raman spectroscopy[3] and for the phenyl boronate ion, because the acidity is diminished by *ortho*-substitution (F-strain)[4] and increased by the addition of polyols.[5] Lorand and Edwards[5] found that the formation constants of complexes between phenyl boronic acid and various polyols were larger than those of the corresponding boric acid–polyol complexes, and deduced that the phenyl boronate ion was tetrahedral. The

[1] Part XI: M. J. S. Dewar and V. P. Kubba *J. Amer. Chem. Soc.* In press.
[2] H. R. Snyder, A. J. Reedy and W. J. Lennarz *J. Amer. Chem. Soc.* **80**, 835 (1958); W. J. Lennarz and H. R. Snyder, *Ibid.* **82**, 2172 (1960).
[3] J. O. Edwards, G. C. Morrison, V. F. Ross and J. W. Schultz *J. Amer. Chem. Soc.* **77**, 266 (1955).
[4] D. H. McDaniel and H. C. Brown *J. Amer. Chem. Soc.* **77**, 3757 (1955).
[5] J. P. Lorand and J. O. Edwards *J. Org. Chem.* **24**, 769 (1959).

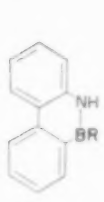
essential reaction was assumed to be of the following type:



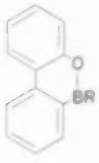
II

They found that the pH-depression tended to a maximum with increasing polyol concentration only in the case of mannitol and ascribed this behavior to the formation of neutral as well as anionic complexes.

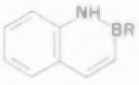
The acidity of derivatives of the heteroaromatic boron containing analogues of phenanthrene (III)[6] (IV)[7] and naphthalene (V)[8] described in previous papers in this series is of further interest since the participation of the boron atom in a cyclic conjugated system has been shown[6-8] to modify its properties considerably and should allow ultra-violet spectroscopy to be used to follow the acid-base changes. We have



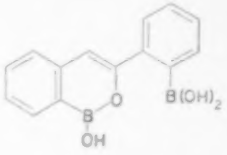
III
a, R = OH



IV
a R = OH



V
a R = OH
b R = Me
c R = Ph



VI

studied three heteroaromatic compounds from this viewpoint, 10-hydroxy-10,9-borazarophenanthrene (IIIa) 10-hydroxy-10,9-boroxarophenanthrene (IVa) and 2-hydroxy-2,1-borazaronaphthalene (Va). The isomerization product of 2,2′ tolandiboronic acid[9] which very probably[7] has the structure (VI) is also discussed and measurements were made on phenyl boronic acid and 2-biphenylboronic acid for comparison. Although Va exists[8] as bis(2,1-borazaro-2-naphthyl)ether in the solid state and IVa undergoes reversible dehydration, the formation of alkyl ethers[8,10] from IIIa, IVa and Va on crystallization from alcohols and the ease of their hydrolysis shows that all three exist as hydroxy-derivatives in solution in aqueous ethanol.

The acidities were compared as the pH-values of half-neutralized solutions of the acids in 1:1 aqueous ethanol. The point of half-neutralization was the calculated one since most of the acids were too weak to allow an accurate determination of the end-points in this solvent mixture. The effect of polyol was found by adding mannitol in concentrated aqueous solution at the half-neutralization point.

[6] M. J. S. Dewar, V. P. Kubba and R. Pettit *J. Chem. Soc.* 3073 (1958).
[7] M. J. S. Dewar and R. Dietz *J. Chem. Soc.* 1344 (1960).
[8] M. J. S. Dewar and R. Dietz *J. Chem. Soc.* 2728 (1959).
[9] R. L. Letsinger and J. R. Nazy *J. Amer. Chem. Soc.* **81**, 3013 (1959).
[10] M. J. S. Dewar, R. Dietz, V. P. Kubba and A. R. Lepley *J. Amer. Chem. Soc.* In press.

The pH-values of half-neutralized solutions of IIIa and Va did not differ significantly from those of the correspondingly diluted alkali and no increase in acidity was produced by added mannitol. Addition of alkali to an ethanol solution of Va produced a reversible spectral change (Fig. 1) but not in the direction of the corresponding 2-aminostyrene spectrum. No spectral change was produced when alkali was added to ethanolic solutions of 2-methyl and 2-phenyl-2,1-borazaronaphthalene (Vb,c). The reversible reaction of Va with alkali was therefore not one of co-ordination and the anion corresponding to Va must be planar. This reversal of the behavior

Absorption maxima in ultraviolet spectra of

in ethanol	with alkali	in ethanol
223mμ		224mμ
	232mμ	
		258
264	265	
273	275	
313		318
324	324	
	333	

FIG. 1. Effect of added alkali on ultraviolet spectrum of a bis (2,1-borazaro-2-naphthyl)ether.

in acyclic boronic acids is compatible with the aromatic formulation of Va. The addition of a hydroxyl ion would remove the boron atom from conjugation and any aromatic stabilization energy would be lost. Similarly no change is produced in the spectra of any available 2,1-borazaronaphthalene by the addition of acid. The extreme weakness of the acids (IIIa and Va) may be explained likewise. Removal of a proton leaves a negative charge on the oxygen atom which reduces the extent of charge transfer from nitrogen to boron necessary for aromaticity. The annular boron atom in VI was reported[9] to show no acidity, even in the presence of mannitol, and this unexplained observation is clearly capable of similar rationalization.

The pH-values of half-neutralization of phenyl boronic acid, 2-biphenyl boronic and IVa were 11·0, 12·0 and 9·1 units. The difference between the first two was compatible with F-strain in the 2-biphenyl boronate ion, but the acidity of IVa was surprisingly high. It appears[11] to be one of the strongest boronic acids known and presents a most striking contrast to the behavior of the boron-nitrogen heterocycles discussed above, and particularly to that of VI. The acidities of IVa and the two acyclic boronic acids were increased by added mannitol. The resulting pH-depressions are shown (Fig. 2), and in each case tended towards a maximum.

The ultraviolet spectrum of 10-hydroxy-10,9-boroxarophenanthrene was measured with an excess of mannitol in neutral, acidic, and basic solution (Fig. 3). Under acidic conditions the spectrum was exactly like that in the absence of mannitol. No

[11] G. E. K. Branch, D. L. Yabroff and B. Bettman *J. Amer. Chem. Soc.* **56**, 937 (1934).

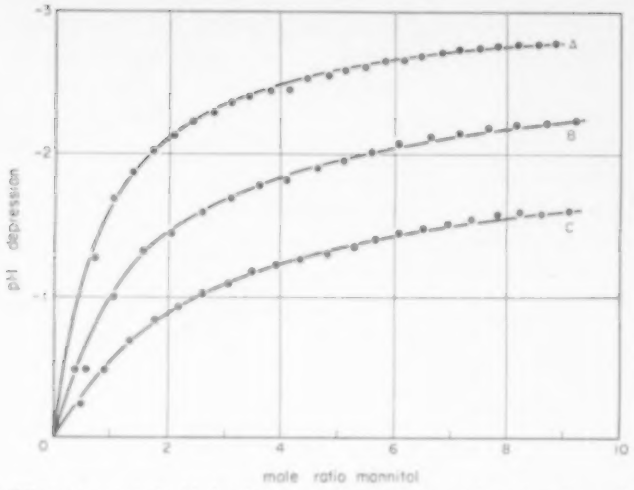


FIG. 2. Effect of mannitol added to half-neutralized solutions of A, phenylboronic acid; B, 2-biphenylboronic acid; C, 10-hydroxy-10,0-boroxarophenanthrene in 1:1 aqueous ethanol.

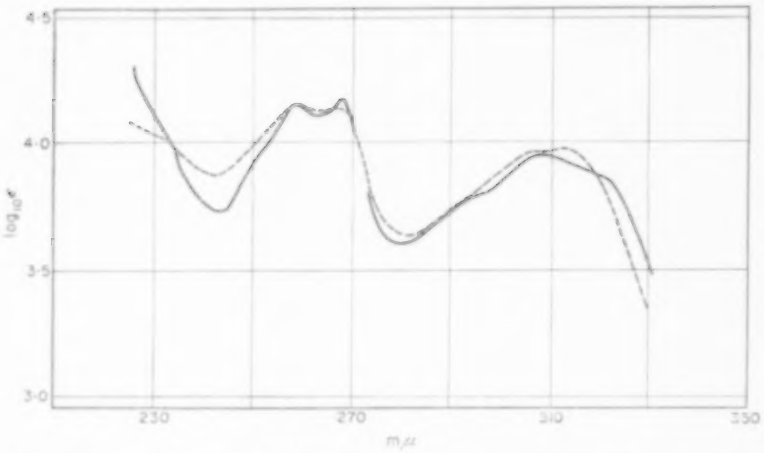


FIG. 3(a). Ultraviolet spectra of 10-hydroxy-10,9-boroxaropehnanthrene in 95 per cent ethanol with alkali (. . . .) and with aqueous mannitol (———).

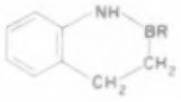
Absorption maxima in the ultraviolet spectrum of 10-hydroxy-10,9-boroxarophenanthrene in

Ethanol (mμ)	Ethanol with alkali (mμ)	Ethanol with mannitol (mμ)	Ethanol with acid and mannitol (mμ)
258		259	258
	260		
	267		
268			268
		269	
283			283
294			294
		309	
	310		

FIG. 3(b). Effect of added mannitol on ultraviolet spectra of 10-hydroxy-10,9-boroxarophenanthrene.

neutral complexes were formed. The neutral spectrum, however, resembled closely that of the anion; this was produced[7] reversibly by the addition of a little alkali to a solution of IVa, and reverted to the original spectrum with acid. The alkaline spectrum in presence of mannitol was very similar. Anionic complexes were therefore formed between IVa and mannitol. Their spectral similarity to the simple anion leaves little doubt that the ionic equilibria must resemble those of equation (II) and that the boron atom is tetrahedral and removed from conjugation in the anion. The only possible rationalization of the unusual acid strength of IVa and the total dissimilarity from VI is that the boroxarophenanthrene system is quite highly strained, as indeed is indicated by models, and that the strain is relieved when the boron atom adopts a tetrahedral configuration. The explanation given earlier[7] of the reduced aromaticity of the 10,9-boroxarophenanthrenes may well require modification and further work on the boroxaronaphthalenes is clearly necessary since the reported[9] lack of acidity of the annular boron atom in VI suggests that they resemble the 2,1-borazaronaphthalenes quite closely.

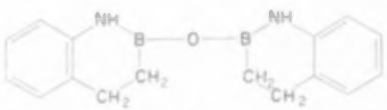
Further confirmation of the aromatic formulation of the latter compounds V has now been obtained. We hoped to reduce the non-benzenoid double bond to give derivatives of 3,4 dihydro-2,1-borazaronaphthalene (VI), and to demonstrate the unusual properties of IV were dependent on 3,4 unsaturation.



VII

Bis(2,1-borazaro-2-naphthyl) ether (VIII) proved to be fairly resistant to treatment which lead to the smooth reduction of most styrenes.[12] Recovery was 70 per cent when a 6-molar excess of sodium was added to a boiling solution of VII in ethanol. When n-butanol was used, bis(3,4-dihydro-2,1-borazaro-2-naphthyl)ether (IX) was formed in good yield. The structure of the product followed from elementary

VIII



IX

analysis; the identification in the infrared spectrum (Fig. 4) of peaks due to the stretching of aliphatic C—H-bonds (2915, 2882, 2825 cm^{-1}), absent in the spectrum of VIII, and of an N—H bond (3378 cm^{-1}); and the ultraviolet spectrum (Fig. 5) which resembled that of a 2-toluidine rather than that of VIII. An analogous reduction of 2-naphthol with sodium in amyl alcohol to give 2-hydroxy-1,2,3,4-tetrahydro naphthalene has long been known.[13]

When warmed in acetic anhydride (IX) gave a diacetyl derivative (X) as shown by elementary analysis and the absence of an NH stretching absorption in the I.R. spectrum (Fig. 4). After similar treatment VIII was recovered unchanged.

[12] K. N. Campbell and B. K. Campbell *Chem. Rev.* **31**, 85 (1942).
[13] E. Bamberger and W. Lodter *Ber.* **23**, 197 (1890).

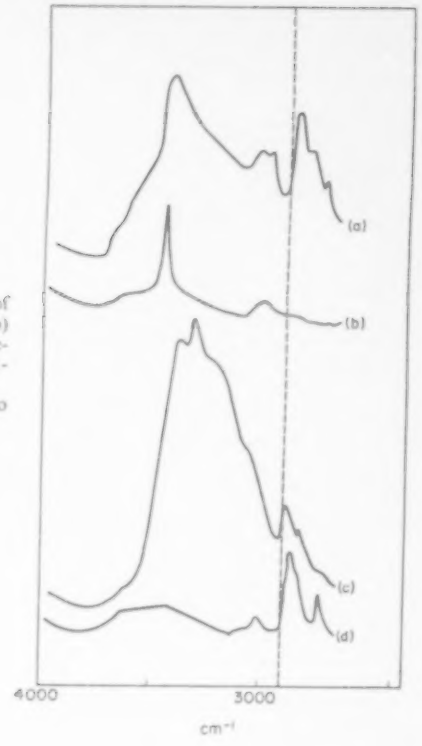


FIG. 4. Infrared spectra in hexachlorobutadiene mulls of (a) bis (3,4-dihydro-2,1-borazaro-2-naphthyl) ether; (b) bis (2,1-borazaro-2-naphthyl) ether; (c) 2-acetamidophenethyl boronic acid; (d) bis (1-acetyl-3,4-dihydro-2,1-borazaro-2-naphthyl) ether.
Absorption to the right of the broken line corresponds to saturated C—H stretching.

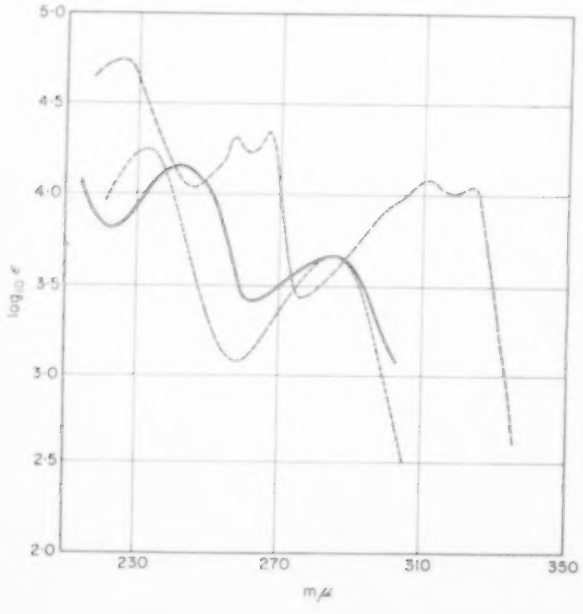
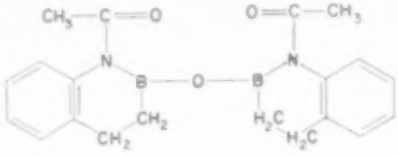


FIG. 5. Ultraviolet spectra of bis (3,4-dihydro-2,1-borazaro-2-naphthyl) ether in cyclohexane (———) of bis (2,1-borazaro-2-naphthyl) ether in cyclohexane (– – –) and of 2-toluidine in cyclo-octane with concentration doubled (. . . . .).

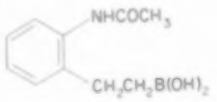
The unusual resistance to hydrolysis of the boron-nitrogen bond in the 2,1-borazaronaphthalenes was strongly indicative of their aromaticity. 2-Phenyl-2,1-borazaronaphthalene (Vc) was recovered unchanged after 3 hr boiling with concentrated hydrochloric acid and after 2 hr boiling with 40 per cent aqueous potassium hydroxide. Prolonged boiling of VIII in 10 per cent aqueous alkali[8] failed to produce an ultraviolet spectrum different from that of the anion, which was produced immediately and reversibly by the addition of a little alkali to an ethanolic solution.



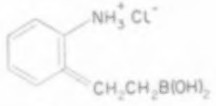
X

The stability of the boron–nitrogen bonds in IX and X was of a quite different order. Their melting points fell on storage in air, but returned to the original values after heating *in vacuo*. X dissolved in hot water and there crystallized a new compound, whose neutralization equivalent differed from that of X by the equivalent of 1·5 molecules of water. The infrared spectrum (Fig. 4) unlike that of X showed a broad N—H stretching absorption at 3336 cm^{-1}, and elementary analysis supported the formulation 2-acetamidophenethylboronic acid (XI). No sharp melting point could be obtained for XI, even in preheated baths, presumably because of slow cyclization to (X). On heating XI *in vacuo*, reconversion to (X) was quantitative.

2-Amino phenethyl boronic acid hydrochloride (XII) crystallized from solutions of IX in dilute hydrochloric acid. Cyclization of XII was apparently inhibited by the positive charge on the nitrogen atom, since a sharp melting point was observed and since no dehydration could be effected by heating *in vacuo*.

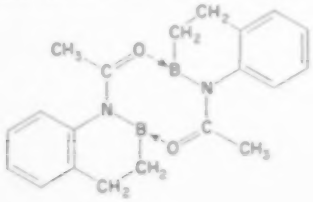


XI

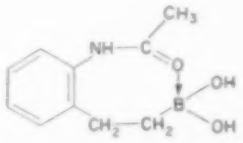


XII

One curious feature of X and XI was that their IR spectra showed no amide carbonyl absorption (1625–1700 cm^{-1}), although their preparation and interconversion leave their structures in no doubt. The only reasonable explanation seems to be that the carbonyl groups are internally chelated to boron (XIII and XIV), and that the weakened carbonyl absorption then appears at lower frequencies. The structures (XIII and XIV) are conformationally favorable and little strained.

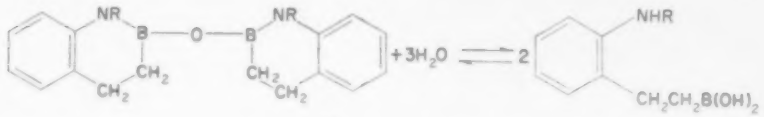


XIII



XIV

Reduction of the 3,4-double bond in the 2,1-borazaronaphthalenes resulted in a considerable modification in the properties of the system. The stability of the boron–nitrogen bond was reduced to an extent such that the reversible reaction (XV) took place, and acetylation of the amine function under normal conditions became possible,



XV

whereas we were unable to prepare an acetyl derivative of VIII. Both differences clearly reflected the aromaticity of the 2,1-borazaronaphthalenes.

EXPERIMENTAL

Acid strengths

Samples (ca. 25 mg) of the various acids were dissolved in a mixture of carbon dioxide-free water (25 ml) and ethanol (25 ml) at 15°. A slow stream of nitrogen was passed through the solution, and successive equal volumes of sodium hydroxide (0·05 N in CO_2-free water) and ethanol were added. The pH-value of the solution was measured after each pair of additions by means of a Pye Universal pH meter, with micro calomel and glass electrodes. The meter was standardized in a pH 5·6 aqueous buffer and the electrodes were stored in water and immersed in the solvent mixture for the minimum time consistent with accuracy. The difference in buffer readings before and after the titration never exceeded 0·02 pH units for the quoted values. Mannitol was added dropwise in 10 per cent aqueous solution. Duplicate determinations were carried out in all cases, the deviation never exceeding 0·05 pH units for the quoted values.

Neutralization equivalents were found by titration with standard alkali in the presence of mannitol. Bis(2,1-borazaro-2-naphthyl)ether was prepared from 2-amino styrene.[8] Analyses, including those for boron, were by Alfred Bernhardt, Mulheim, Germany.

Bis(3,4-*dihydro*-2,1-*borazaro*-2-*naphthyl*) *ether*

Freshly cut pieces of sodium (2·3 g; 0·1 g atoms) were added down the condenser to a vigorously stirred, boiling solution of bis(2,1-borazaro-2-naphthyl) ether (4·11 g, 0·015 mole) in n-butanol (300 ml). When the sodium had dissolved, water (500 ml) and hydrochloric acid were added until the aqueous layer was strongly acid. The butanol–water azeotrope was removed at 100° and *c.* 30 mm before the red solution was cooled, made just alkaline with ammonia (sp.gr. 0·880) and extracted with ether (5 × 100 ml). The combined ethereal extracts were dried ($MgSo_4$) and evaporated to give a red oil which, when heated at 80° and 0·5 mm gave crude *bis* (3,4-*dihydro*-2,1-*borazaro*-2-*naphthyl*)*ether* as a pale yellow solid, m.p. 83–86° (3·8 g, 91%).

Crystallization under dry nitrogen from dry pentane removed the color and raised the melting point to 87·5–89°.

(Found: C, 69·6; H, 6·5; N, 10·0; B, 8·0%. Calc. for $C_{16}H_{18}N_2B_2O$ C, 69·6; H, 6·6; N, 10·2; B, 8·0%.

Bis(1-*acetyl*-3,4-*dihydro*-2,1-*borazaro*-2-*naphthyl*)*ether*.

The diacetyl derivatives was formed on warming bis(3,4-dihydro-2-1-borazaro-2-naphthyl)ether in acetic anhydride. Hydrolysis was avoided by removing the excess of reagent at 100° and 15 mm. Crystallization from chloroform–light petroleum (b.p. 60–80°) gave needles of the diacetyl derivative m.p. 280–282°.

(Found: C, 66·6; H, 6·2; N, 7·7; B, 6·4%. Neutralization equivalent 180.) Calc. for $C_{20}H_{22}N_2B_2O_3$ C, 66·7; H, 6·2; N, 7·8; B, 6·0%. Neutralization equivalent 181.

2-Acetamido phenethyl boronic acid

Crystallization of the above diacetyl derivative from water gave rectangular prisms of *2-acetamido phenethyl boronic acid*, which began to melt at 127°. No sharp melting point could be obtained, even in preheated baths.

(Found: C, 58·3; H, 6·8; N, 7·0; B, 5·5%. Neutralization equivalent 208. Calc. for $C_{10}H_{14}NO_3B$ C, 58·0; H, 6·8; N, 6·8; B, 5·2%. Neutralization equivalent 207.)

2-Amino phenethyl boronic acid hydrochloride

Crystallization of bis(3,4-dihydro-2,1-borazaro-2-naphthyl)ether from dilute hydrochloric acid (2 N) after treatment with charcoal gave long colorless needles of the *hydrochloride* m.p. 190–192°.

(Found: C, 47·3; H, 6·5; N, 7·0; Cl, 17·7; B, 5·7%. Calc. for $C_8H_{12}NClO_2BC$, 47·7; H, 6·5; N, 7·0; Cl, 17·6; B, 5·4%.)

Acknowledgements—The work described in this paper was carried out at Queen Mary College, University of London. We wish to thank the University of London for the award of the William Lincoln Shelley Research Studentship (to R. D.) the Kodak Co. for the gift of crude 2-aminophenethanol, and Dr. J. M. Davidson for a sample of 2-biphenyl boronic acid.

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NEW HETEROAROMATIC COMPOUNDS—XIII[1]

REACTIONS OF 10-SUBSTITUTED 9-ETHOXYCARBONYL-10:9-BORAZAROPHENANTHRENES

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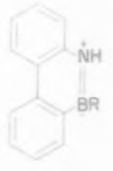
George Herbert Jones Laboratory, University of Chicago

(*Received* 18 *February* 1961)

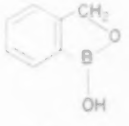
Abstract—10-Ethoxycarbonyl derivatives of 10:9-borazarophenanthrenes have been prepared by reaction of the 10-lithio derivatives with ethyl chloroformate. Unlike the parent compounds they are rapidly oxidized by air to products in which the BN bond is broken. These reactions suggest that the stability of the present compounds to oxidation and hydrolysis must be due to resonance stabilization. A measurement of the dipole moment of 10-methyl-10:9-borazarophenanthrene by Professor R. Huisgen and his collaborators is reported.

PREVIOUS papers of this series have described a number of novel heterocyclic boron compounds isoconjugate with normal aromatic hydrocarbons. These compounds showed much greater stability than previously described organic compounds of boron and this was taken as evidence for aromaticity. Two lines of evidence have suggested however, that this may not be the case and that the resonance effects in such compounds may be small.

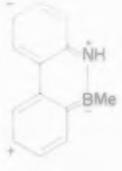
In the first place Professor R. Huisgen has informed[3] us that one of these compounds, 10-methyl-10:9-borazarophenanthrene (I), has a very low dipole moment (0·16 ± 0·02D), suggesting that the contribution of dipolar resonance structures such as (I) must be small. Secondly Snyder and his collaborators[4] have reported that the cyclic boric ester (III) is very resistant to hydrolysis, suggesting that the stability of our compounds might be due merely to their cyclic structure.



I, R=Me
II, R=Ph



III



IV

If the stability of compounds such as (I) is due to aromaticity, the stability should be reduced by structural changes which destroy the resonance in the boron-containing rings. This could be effected in (I) by attaching +E substituents to nitrogen or −E

[1] Part XII: M. J. S. Dewar and R. Dietz, previous paper.
[2] Present address: Department of Chemistry, Cornell University, Ithaca, New York
[3] Details are given in a note at the end of this paper at Professor Huisgen's request.
[4] H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Amer. Chem. Soc.* **80**, 835 (1958); W. J. Lennarz and H. R. Snyder, *Ibid.* **82**, 2172 (1960).

substituents to boron; for the resonance interaction between nitrogen and a +E substituent (e.g. acyl) should reduce the availability of the p-electrons of nitrogen for bonding to boron, while −E substitutents (e.g. hydroxy) attached to boron should reduce its tendency to accept electrons from nitrogen. We therefore decided to examine the properties of 9-acyl derivatives of 10:9-borazarophenanthrene.

In a previous paper of this series we reported[5] that the 9-lithio derivatives (V), (VI) of 10-methyl-(I) and 10-phenyl-(II) 10:9-borazarophenanthrene reacted with dimethyl

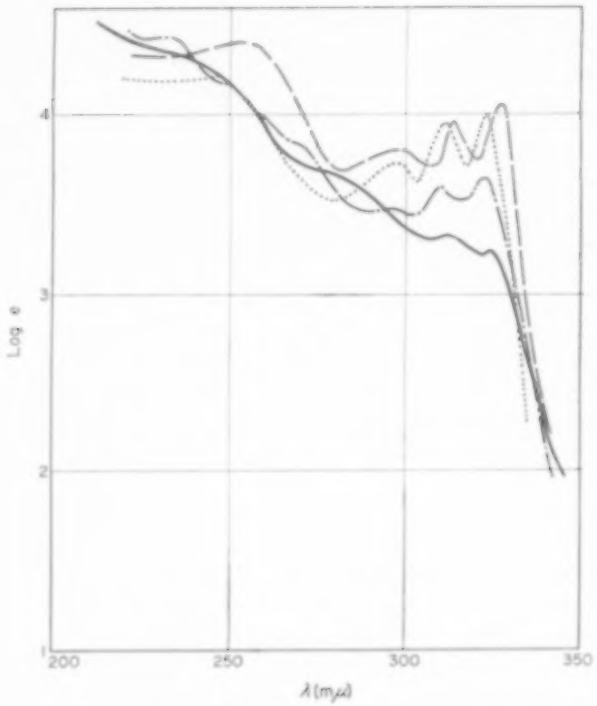


FIG. 1. Comparison of the ultraviolet spectra of 10:9-borazarophenanthrene (IX) (———); (X) (— — —); (I) (– – –); (II) (. . . . .).

sulphate to form the corresponding 9-methyl derivatives (VII), (VIII). We have found that the 9-lithio derivatives react likewise with ethyl chloroformate giving the corresponding urethanes (IX) (X).

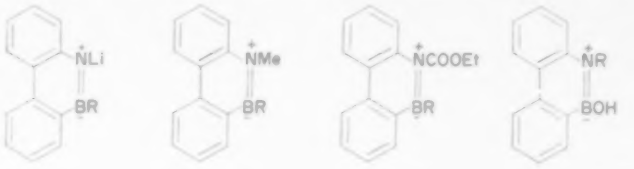
These were reasonably stable compounds, being unaffected by small amounts of alkali or acid in alcoholic solution, and their ultraviolet spectra showed a close similarity to those of the parent compounds (I) or (II) (Fig. 1). Hydrolysis with alkali regenerated (I) or (II) by decarboxylation of intermediate carbamic acids.

However the urethanes (IX), (X) were rapidly oxidized on exposure to air unlike the parent compounds (I), (II), or their 9-methyl derivatives (VII), (VIII). The liquid 10-methylurethane (IX) gave a solid oxidation product (A). The crystalline 10-phenylurethane (X) was stable in air but an ethereal solution underwent oxidation to

[5] M. J. S. Dewar and P. M. Maitlis, *J. Amer. Chem. Soc.* **83**, 187 (1961).

phenol and the same product (A) that had been obtained from (IX). Clearly the oxidation must have led to loss of the methyl or phenyl group from boron.

The oxidation product (A) was clearly closely related to 10-hydroxy-9-ethoxycarbonyl-10:9-borazarophenanthrene (XI) since it contained the correct amount of



V, R=Me VII, R=Me IX, R=Me XI, R=COOEt
VI, R=Ph VIII, R=Ph X, R=Ph XII, R=H

ethoxyl and it was readily hydrolyzed by alkali to 10-hydroxy-10:9-borazarophenanthrene (XII). However, the ultraviolet spectrum (Fig. 2) no longer showed the

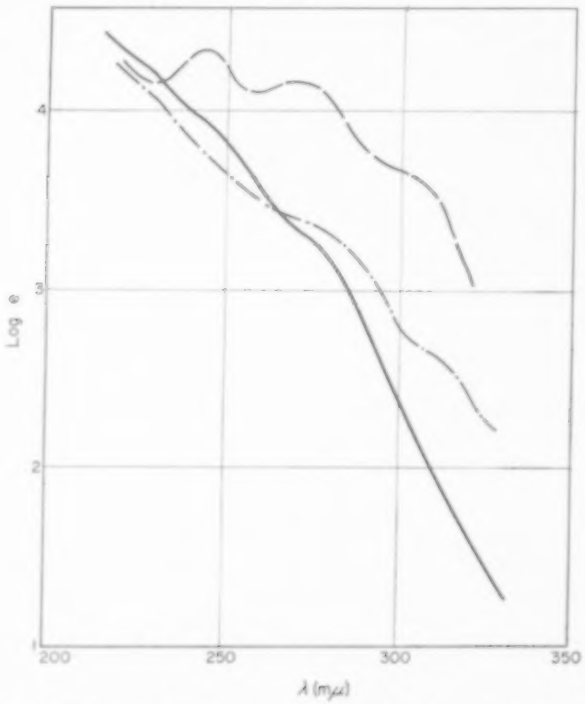
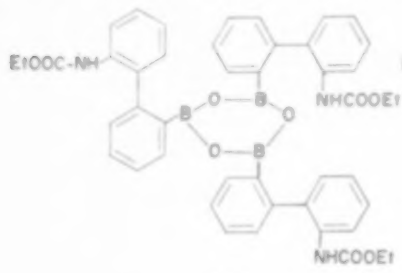


FIG. 2. Comparison of the ultraviolet spectra of (A) in 95% ethanol (———) and in 95% ethanol containing sodium hydroxide (– – –) with that of 2-methylbiphenyl-2'carboxamide (— — —).

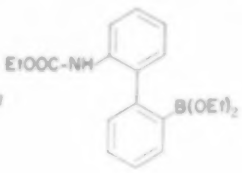
absorption in the 320 mμ region characteristic of 10:9-borazarophenanthrene derivatives; indeed it showed no peaks at all above 225 mμ, rising steadily from 330 mμ (log E, 2·25) to 225 mμ (log E, 4·46) through a series of shallow inflections. This type of spectrum is characteristic of a sterically hindered diphenyl, with an auxochromic

group attached to one ring; 2-methylbiphenyl-2′-carboxamide shows a spectrum very similar[6] to that of (A).

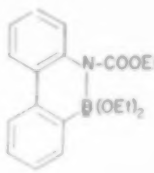
This strongly suggested that (A) no longer had an intact B–N bond, a conclusion supported by the infrared spectrum which showed a very broad NH band at 2·97 μ and a carbonyl band at 5·9 μ; absorption of this type is characteristic of a urethane. The 9-ethoxycarbonyl derivatives (IX), (X) showed carbonyl absorption at 5·75 μ; here the conjugative interaction between nitrogen and carbonyl is less than in a normal urethane since the nitrogen forms part of an aromatic ring. The infrared spectrum of (A) also showed a single peak at 7·45 μ, presumably due to B–O stretching, and also a strong band at 14·4 μ analogous to that observed[7] in arylboronic anhydrides. This evidence suggests that (A) was 2′-ethoxycarbonamido-2-biphenylboronic anhydride (XIII) which presumably forms the corresponding ethyl ester (XIV) in alcoholic solution. This formulation was further supported by the appearance of definite peaks (Fig. 2) in the ultraviolet spectrum at 250–260 mμ when alkali was added to the alcoholic solution; peaks in this region are characteristic[8] of an unhindered biphenyl, suggesting that alkali brings about a cyclization of (VI) to the planar ion (VII).



XIII



XIV



XV

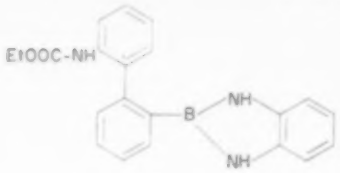
Similar ions were probably formed when (A) dissolved in aqueous alkali; (A) was precipitated unchanged from such solutions by acidification. Moreover (A) reacted with O-phenylenediamine in the manner typical[9] of arylboronic anhydrides to form the diazborole derivative (XVI) which had a strong carbonyl band at 5·8 μ.

One aspect of (A) proved puzzling. The strength of the NH and CO bands in the infrared (KBr disc) varied greatly in different samples and the analyses were erratic. We eventually found that prolonged drying in a vacuum at 214° (just below the melting point) gave material (B) which showed no absorption in the regions normally characteristic of imino or carbonyl groups and which analyzed for (XIII) less half a molecule of water per biphenyl residue. This indicated that (XIII) must have undergone dehydration. The most likely structure for the product is the *bis* carbethoxyanhydride structure (XVII). The lack of a normal carbonyl band in the infrared can be ascribed to internal coordination to (XVIII) (cf. the preceding paper). Models indicate that the chelate structure (XVIII) should be almost unstrained. The formation of (XVIII) from (XIII) is easily understood; most preparations are evidently mixtures of

[6] R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds* No. 181. John Wiley, New York (1951).
[7] H. R. Snyder, M. S. Konecky and W. J. Lennarz, *J. Amer. Chem. Soc.* **80**, 3611 (1958).
[8] cf. C. H. Beaver, D. M. Hall, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.* 854 (1952); G. H. Beaver and D. M. Hall, *Ibid.* 4638 (1956).
[9] cf. R. L. Letsinger and S. B. Hamilton, *J. Amer. Chem. Soc.* **80**, 5411 (1958).

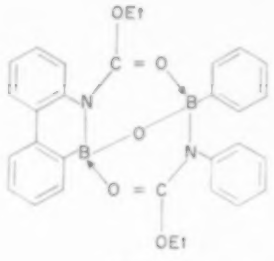
the two. Fresh material that had been only gently dried gave very strong imino and carbonyl absorption and its analysis corresponded closely to (XIII).

The structure of (XIII) was further indicated by a synthesis from 10-hydroxy-10:9-borazarophenanthrene (XII) by treatment with slightly more than two moles of phenyllithium, followed immediately by an excess of ethyl chloroformate. If (XII) is



XVI

XVII

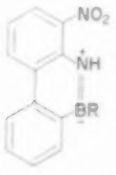


XVIII

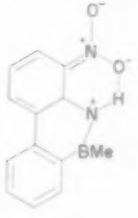
allowed to stand with an excess of phenyllithium the hydroxyl is replaced by phenyl giving (II); reactions of this kind are also effected[10] by the action of Grignard reagents on (XII).

We also examined the reactions of benzoyl chloride with the 9-lithio derivatives (V) and (VI). In each case the same high-melting product was formed, suggesting

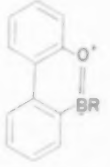
XIX



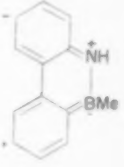
XX, R=Me
XXI, R=OH



XXII



XXIII, R=Ph
XXIV, R=OH



XXV

that the methyl or phenyl group had been lost during the reaction. The reaction product was insoluble in all solvents (except concentrated sulfuric acid which destroyed it) and the infrared spectrum (KBr disc) showed the carbonyl absorption at 6·1 μ characteristic of aromatic amides together with a very broad NH band. Analogy suggests that the product was a mixture of benzamido derivatives analogous to the urethanes (XIII) and (XVII), formed by oxidative demethylation or dephenylation of intermediate 10-benzoyl derivatives (XIX). All attempts to isolate (XIX) failed; unless

[10] M. J. S. Dewar, R. Dietz, Ved P. Kubba and A. R. Lepley, *J. Amer. Chem. Soc.* In press (1961).

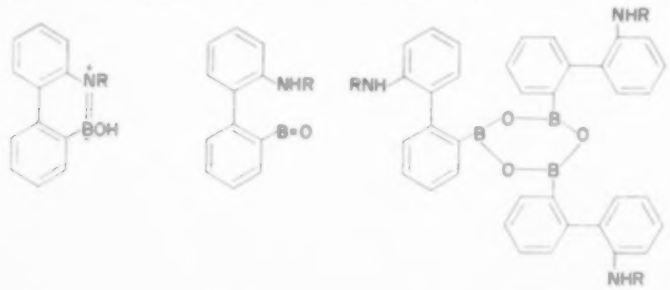
these compounds are not formed, which seems unlikely, they must be much more susceptible to oxidation than the corresponding urethanes (XI), (X).

These results suggest very strongly that the stability of compounds such as (I) to oxidation or hydrolysis is not due simply to their cyclic structure but must be ascribed to resonance stabilization. Introduction of electron-attracting substituents such as ethoxycarbonyl or benzoyl into a molecule would normally decrease its ease of oxidation. Such substituents attached to the nitrogen atom of borazarophenanthrene should, however, reduce the resonance stabilization of the central ring and benzoyl should have a greater effect than ethoxycarbonyl in view of its greater +E activity. If the stability of (I) is due to resonance stabilization, the ease of oxidation should therefore rise in the series (I), (II), < (VI), (VII) < (XIX), as observed. It is also interesting that the B–N bond of borazarophenanthrene remains intact in the 10-hydroxy derivative (XII) and in the 9-ethoxycarbonyl derivatives (IX), (X), but breaks easily in the 10-hydroxy-9-ethoxycarbonyl derivative (XI). If the stability of these compounds to hydrolysis were due solely to their cyclic structures this would be difficult to explain. If however the stability is due to resonance it should be decreased both by +E substituents (e.g. COOEt) attached to nitrogen and by −E substituents (e.g. OH) attached to boron. The BN bond can apparently survive one such substitution but not both simultaneously.

A similar effect should be observed when the ring adjacent to nitrogen carries +E substituents. This seems to be the case. Thus while neither 10-methyl-10:9-borazarophenanthrene (I) nor its 6-nitro derivative are demethylated during nitration with acetic anhydride and nitric acid, the 8-nitro derivative (XX) undergoes partial oxidation to 10-hydroxy-8-nitro-10:9-borazarophenanthrene (XXI).[11] In the 8-nitro derivative there is a strong interaction between the imino nitrogen and the nitro group which can be represented as a contribution by the dipolar resonance structure (XXII). The corresponding structure (XIV) for the 6-nitro derivative is less important since it involves greater charge separation and since there is no possibility of hydrogen bonding between NH and NO_2 (cf. (XXII)).

A similar effect again should be brought about by replacing nitrogen in (I) by a more electronegative atom such as oxygen. This is indeed so; 10-phenyl-10:9-borazarophenanthrene (XXIII) is rapidly oxidized by air to the corresponding 10-hydroxy derivative (XXIV) which can be isolated as its anhydride.[12]

These arguments imply that (I) would undergo rapid oxidation were it not for



XVI XVII XVIII

[11] M. J. S. Dewar and Ved P. Kubba, *Tetrahedron* **7**, 213 (1959).
[12] M. J. S. Dewar and R. Dietz, *J. Chem. Soc.* 1344 (1960).

strong resonance interactions in the central ring. The resistance to oxidation is therefore strong evidence that compounds of this type are aromatic.

The relation between (IVc) and (V) is interesting. Any 10-hydroxy-10:9-borazarophenanthrene (XVI) is isomeric with an arylboron oxide (XVII), the trimer of which is an arylboronic anhydride (XVIII).

The relative heats of formation of (XVI) and (XVIII) will depend on their total bond energies and resonance energies; if the former could be estimated, one might be able to draw conclusions concerning the resonance energy of (XVI) from the relative stabilities of (XVI) and (XVIII). Unfortunately this is not possible since the B–N bond energy is known only in borazine derivatives where there is an uncertain correction for the resonance energy of the borazine ring; the experimental evidence suggests that (XVI) is normally the more stable form, but that introduction of + E substituents on the nitrogen atom makes (XVIII) more stable. Such substituents should decrease the resonance energy of (XVI), but not that of (XVIII).

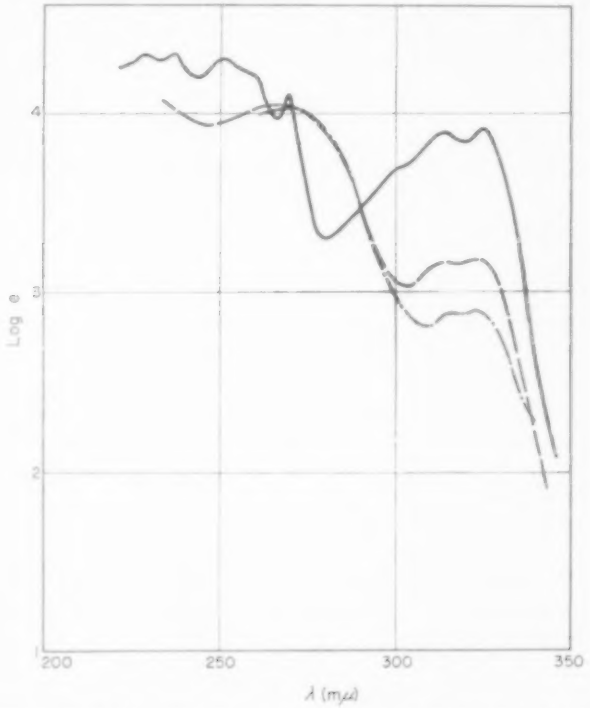


FIG. 3. Comparison of the ultraviolet spectra of XII in 95% ethanol (——) and in a mixture of 95% ethanol with concentrated hydrochloric acid, either 1:5 v/v (– – –) or 1:10 v/v (— · — · —).

The reactions of borazarophenanthrenes with acid are interesting. Derivatives with a free NH group seem to undergo protonation in acid without rupture of the central ring; this is indicated in the ultraviolet spectrum by the disappearance of the typical borazarophenanthrene bands in the 320 mμ region and the appearance of the strong maximum round 260 mμ characteristic of a planar unhindered biphenyl (cf. Fig. 3). The urethanes (IX), (X) also undergo protonation in strong acid, but the

ultraviolet spectrum now loses all its structure (Fig. 4), showing the characteristics of a sterically hindered biphenyl. This must mean that the central ring of (IV) undergoes rupture under these conditions. Presumably protonation takes place first on the carbonyl oxygen. This increases the +E activity of the group to such an extent that the central ring loses all its aromatic character and so undergoes hydrolysis. The urethane must have remained intact during the time that it took to measure the

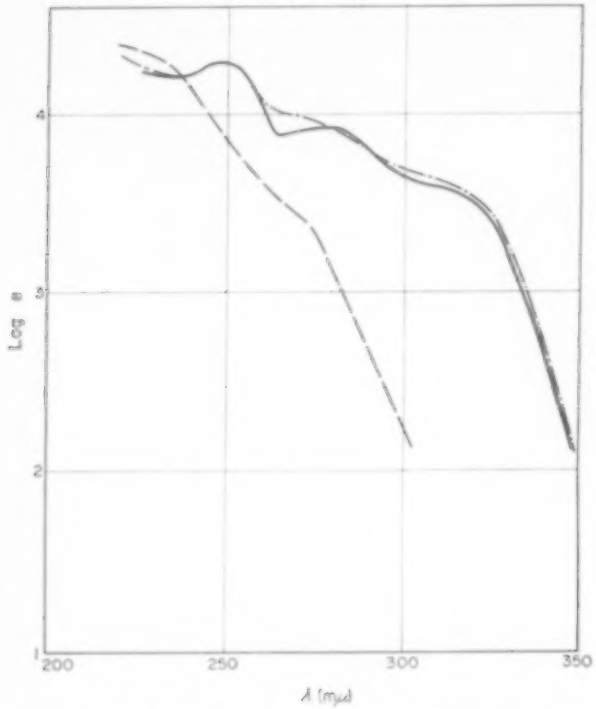


FIG. 4. Comparison of the ultraviolet spectra of X in alkaline ethanol (——) and in a mixture of 95% ethanol with concentrated hydrochloric acid, 1:5 v/v (– – –), with that of IX in alkaline ethanol (— · — · —).

spectrum since hydrolysis would have led to ring closure to 10-phenyl-10:9-borazarophenanthrene which like the 10-hydroxy derivative forms salts in which the central ring is intact.

EXPERIMENTAL

The infrared spectra were measured on a Grubb-Parsons double beam spectrophotometer; ultraviolet spectra in 95% ethanol on a Unicam S.P. 500 spectrophotometer. The ultraviolet spectra in strong acid were carried out on ethanolic solutions of the B-hydroxy compounds which were diluted with concentrated hydrochloric acid (1:5 for the 9·0 N and 1:10 for the 9·8 N solutions). The microanalyses were carried out by Alfred Bernhardt, Mülheim, Germany; molecular weights were determined in naphthalene since camphor did not give reliable results.

9-Ethoxycarbonyl-10-methyl-10:9-borazarophenanthrene (IVb). A solution of 10-methylborazarophenanthrene[24] (7·0 g; 0·0363 mole) in benzene (30 ml) was titrated under nitrogen with an ethereal solution of methyllithium (it required 34 ml (0·048 mole) of a solution containing 0·5 g active lithium per 50 ml). The end-point of the titration was marked by the appearance of a stable bright yellow colour.[8] The solution was stirred for 5 min and then a benzene solution of dry, freshly distilled ethyl

chloroformate (5·5 g in 20 ml) was added; the color disappeared immediately and the solution was refluxed for one hour. It was then cooled, hydrolyzed with dilute hydrochloric acid and ether-extracted. The ethereal solution was dried, and the solvent distilled (last traces of ethyl chloroformate being removed under vacuum), to leave an oil which did not solidify on cooling. The oil distilled at 160°/0·3 mm to give, after a small fore-run of starting material, 9-ethoxycarbonyl-10-methyl-10:9-borazarophenanthrene (9·6 g, 80%), $n_D^{21\cdot5}$ 1·6188 (Found: C, 72·37; H, 5·78; N, 5·33; B, 4·41%; M, 268. $C_{16}H_{16}O_2NB$ requires: C, 72·45; H, 6·04; N, 5·28; B, 4·09%; M, 265).

9-*Ethoxycarbonyl*-10-*phenyl*-10:9-*borazarophenanthrene* IVa. A solution of 10-phenylborazarophenanthrene[2a] (5·0 g, 0·0196 mole) in benzene (20 ml) was titrated with ethereal phenyllithium [it required 15 ml (0·0215 mole) of a solution containing 0·5 g. active lithium per 50 ml]. A benzene solution of ethyl chloroformate (4·0 g. in 10 ml) was added, the color diappeared and the solution was refluxed for one hour. It was worked up as previously described to give a brown liquid which solidified on cooling. Crystallization from ether-light petroleum (b.p. 40–60°) gave 9-ethoxycarbonyl-10-phenyl-10:9-borazarophenanthrene (2·6 g) m.p. 116–117°. The mother liquors were chromatographed on alumina and eluted first with ether to give 10-phenylborazarophenanthrene (0.5 g) and then with chloroform to give more ethoxcarbonylphenylborazarophenanthrene (0·7 g) m.p. 113–115°*. The total yield was 3·3 g (51%) (Found: C, 76·1; N, 5·48; N, 4·28; B, 3·15%. M, 320,206. $C_{21}H_{18}O_2NB$ requires C, 77·06; H, 5·50; N, 4·28 B, 3·32%; M, 356).

2-(N-*ethoxycarbonyl*) *aminodiphenyl*-2′-*boronic anhydride* (*Compound* A). A solution in benzene (30 ml) of 10-hydroxy-10:9-borazarophenanthrene (4·2 g; 0·0227 mole), which had been thoroughly dried under high vacuum, was titrated with the ethereal phenyllithium (it required 35 ml (0·05 mole) of a solution containing 0·5 g active lithium in 50 ml) till a stable yellow color had been obtained. During the addition nearly all the solid dissolved initially but was reprecipitated towards the end. Ethyl chloroformate in benzene (4·0 g, in 10 ml) was added very quickly; the solution cleared and was refluxed for one hour. The reaction was worked up as described above, to give a solid which gave, on crystallization from benzene–light petroleum b.p. 100–120°), 2-(N-ethoxycarbonyl) aminodiphenyl-2′-boronic anhydride, m.p. 215–220° (3·1 g, 51%). The freshly prepared material had strong C=O and N–H bands and had the following analysis: (Found: C, 67·90; H, 5·17; N, 5·53; B, 4·05; OEt, 17·15%; M, 703. (IV), $(C_{15}H_{14}O_3NB)_3$ requires: C, 67·41; H, 5·24; N, 5·24; B, 4·06; OEt, 16·85%; M, 800).

[(V), $(C_{15}H_{13}O_2NB)_2$ requires: C, 69·78; H, 5·04; N, 5·43; B, 4·26; OEt, 17·45%; M, 5·16].

A sample which had been dried at 214°/0·2 mm and which had m.p. 220–221° and showed only weak carbonyl and N-H absorption in the infrared had analysis; (Found: C, 69·26; H, 4·88; N, 5·44 B, 4·26%).

This latter sample was presumably mainly in the form of the cyclic compound (IX) whereas the fresh sample was mainly present as (V). Samples which had been vacuum dried under milder conditions showed intermediate analyses.

A mixture of compound (A) (130 mg) and *o*-phenylenediamine (60 mg) was dissolved in benzene (50 ml, b.p. 100–120°) and the solution was evaporated until the volume remaining was about 5 ml. On cooling it deposited white crystals (80 mg; 46%) of the *o*-phenylenediamine derivative of 2-(N-ethoxycarbonyl)-aminodiphenyl-2′-boronic anhydride (IV), m.p. 156–157°. (Found: C, 70·06; H, 5·29; N, 11·51%. $C_{21}H_{20}O_2N_3B$ requires: C, 70·58; H, 5·61; N, 11·76%).

2-(N-*Benzoyl*)-*aminodiphenylboronic anhydride*. 10-Phenyl-10:9-borazarophenanthrene (2·3 g, 0·009 mole) dissolved in benzene (20 ml) was titrated with ethereal phenyllithium (0·012 M) and freshly distilled benzoyl chloride (2·5 g) in benzene (15 ml) added. The solution turned deep red and was refluxed for 75 min. It was then worked up rapidly as previously described to give a crude, red, boron-containing solid. This red color was removed by washing with solvent to leave a white amorphous solid m.p. above 300° (2·8 g, 96%). This solid was unaffected by all organic solvents and by hot concentrated solutions by both alkali and acids with the exception of concentrated sulfuric acid in which it dissolved (however on dilution and basification, no product could be isolated). This material was presumably the 2-(N-benzoyl) aminodiphenylboronic anhydride (X) mixed with some

* It is necessary to carry out all the operations in which ethereal solutions are exposed to air very rapidly; even on standing in air for a few minutes solutions of the ethoxycarbonyl compound turn brown due to oxidation.

of the cyclic compound (XI). [Found: C, 78·61; H, 4·63; N, 5·01; B, 3·50%. ($C_{21}H_{14}O_2NB_2$)(X) requires: C, 78·0; H, 4·33; N, 4·33; B, 3·36%. $(C_{21}H_{13}O_2NB)_2O$(XI) requires: C, 80·2; H, 4·14; N, 4·46; B, 3·46%]. It was not possible to determine either the molecular weight of the substance or the ultraviolet spectrum because of the great insolubility of the compound. The infrared spectrum showed a carbonyl band (6·1 μ), an N-H band (2·93 μ) and a band at 7·05 μ which is presumably the B-O band. An exactly similar reaction starting from 10-methylborazarophenanthrene (2·0 g) gave the above material (identical infrared spectra) in 60% yield (2·0 g).

The hydrolyses of 10-*methyl*-(IVb) *and* 10-*phenyl*-(IVa) 9-*ethoxycarbonyl*-10:9-*borazarophenanthrene and* 2-(N-*ethoxycarbonyl*) *aminodiphenyl-2′-boronic anhydride Compound* (A). 10-Methyl-9-ethoxycarbonyl-10:9-borazarophenanthrene (IVb) (1·4 g) was dissolved in ethanol (10 ml) and added to a solution of a sodium hydroxide (3 g) in water (30 ml) and the solution refluxed overnight. On cooling, 10-methyl-10:9-borazarophenanthrene (0·8 g) m.p. 99–100°, mixed m.p. with authentic material 101–102°). Acidification followed by ether extraction gave additional 0·1 g (total yield 88%). 10-Phenyl-9-ethoxycarbonyl-10:9-borazarophenanthrene (IVa) (0·5 g) was hydrolyzed in the same way to give 10-phenyl-10:9-borazarophenanthrene (0·15 g, 39%; m.p. 106–107°, mixed m.p. with authentic material, 107–108°). Alkaline hydrolysis of 2-(N-ethoxycarbonyl) aminodiphenylboronic anhydride (compound, 0·95 g) under the above conditions gave 10-hydroxy-10:9-borazarophenanthrene (0·6 g, 88%), infrared spectrum identical with that of an authentic sample. The melting point is not a reliable guide to the purity of this material; different samples with very similar infrared spectra had m.ps. from 128–130° to 181–182° (lit. 170°)[24]. This probably reflects changes in the hydration of the material since the high m.p. form was only obtained after vigorous vacuum drying at 170°.

Aerial oxidation of 10-*phenyl-and* 10-*methyl*-9-*ethoxycarbonyl*-10:9-*borazarophenanthrene* (IV). 10-Phenyl-9-ethoxycarbonyl-10:9-borazarophenanthrene (0·5 g) was dissolved in ether (20 ml) and the solution left standing in a loosely stoppered flask at room temperature until all the ether had evaporated (48 hr). A brownish crystalline solid remained which was washed with ether and filtered to give compound (A) (0·35 g, 85%; m.p. and mixed m.p. with authentic material 215–220°). The filtrate was evaporated down to dryness and the residue sublimed onto a cold finger to give a small amount of oil which gave a purple spot test with ferric chloride, identical with that given by a sample of phenol, and had an infrared spectrum (in carbon tetrachloride solution) which was identical with that of phenol. An analogous experiment with 10-methyl-9-ethoxycarbonyl-10:9-borazarophenanthrene (0·95 g) which was left standing for five days under the above conditions gave 0·2 g (20% of compound (A), m.p. 215–220°) the remainder being recovered as starting material.

Acknowledgements—The work described here was carried out at Queen Mary College, University of London. We wish to thank British Petroleum Ltd. for the award of a Fellowship (to P. M. M.) and Mr. P. Cook for determining the infrared spectra.

DIE BESTIMMUNG DES DIPOLMOMENTS DES 10-METHYL-10:9-BORAZAROPHENANTHRENS

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Das Dipolmoment des 10-methyl-10:9-borazarophenanthrens wurde nach der fruher beschriebenen Methode[13] gemessen und errechnet; Losüngsmittel Reinstbenzol.

Bestimmung der Dielektrizitätkonstante:

Molenbruch des Gelosten (γ) × 10^2	0	2·2271	4·5345	6·6697	9·4374
Dielektrizitätkonstante (ε)	2·2726	2·2774	2·2823	2·2869	2·2927

Daraus ergibt sich: $\left(\frac{\partial \varepsilon}{\partial \gamma}\right)_{\gamma=0} = 2{\cdot}125.$

[13] R. Huisgen und H. Walz, *Chem. Ber.* **89**, 2616 (1956); R. Huisgen und H. Ott, *Tetrahedron* **6**, 253 (1959).

Vor und nach der Messung wurde das Gerät mit Butyrolacton getestet.

Dichte-Bestimmung: $\left(\frac{\partial d}{\partial \gamma}\right)_{\gamma=0}$ ergab sich zu 0·481

Die Auswertung erfolgte nach Hedestrand.[14] Fur die Molrefraktion wurde ein Näherungswert von 61·30 verwendet, dem Bindungsrefraktionen von Vogel und Mitarbeiter[15] zu Grunde gelegt wurden.

Daraus ergibt sich: $\mu = 0{\cdot}16 \pm 0{\cdot}02$ D.

[14] G. Hedestrand, *Z. Phys. Chem.* **B2**, 428 (1949).
[15] A. J. Vogel, W. T. Cresswell, G. H. Jeffery und J. Leicester. *J. Chem. Soc.* 514 (1952).

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REACTIONS OF SOME DICARBONYL COMPOUNDS

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(*Received* 20 *February* 1961)

Abstract—The reactions of some halogeno keto-esters and the sodio derivatives of β-dicarbonyl compounds have been investigated.

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IN a recent publication[1] we discussed some aspects of the chemistry of furan tetracarboxylic acid (F.T.C.A.; I; R = H), and in particular the preparation of F.T.C.A. by the hydrolysis of its tetraester, (I; R = Et.). The latter compound may be obtained in very satisfactory yield by the dehydration of the tetraester, variously described as II,[2] III,[3] and IV.[4] Further structures, V and VI, have been suggested as reasonable possibilities.[1,4] We have now shown that the tetraester is V.

The tetraester (V), which gives no ferric reaction, may be conveniently prepared[2] by the addition of bromine to a stirred suspension of ethyl sodio-oxaloacetate in an inert solvent. This is a base catalysed reaction of ethyl bromo-oxaloacetate with ethyl oxaloacetate since we have shown that preformed bromo ester will react with ethyl oxaloacetate in presence of sodium acetate or pyridine to give V.

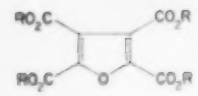
Structures II and III cannot be seriously entertained since both possess an enolizable keto group and would give a ferric reaction. The tetraester (V) shows strong absorption at 3500 cm^{-1}, typical of a single bridge bonded hydroxyl group, but not of an enol. Moreover it is difficult to see how III could cyclize to give I (R = Et), though this reaction has been suggested,[3] and indeed a recent text book[5] draws special attention to it.

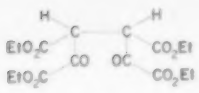
Ethyl bromopyruvate condenses with ethyl sodio-oxaloacetate to give a tricarboxylic ester which has been formulated as VII or VIII. Its formation must proceed by a similar mechanism to that which gives V. Structure VIII and not VII must however represent the triester since on hydrolysis it affords furan 2,3,4-tricarboxylic acid (IX; R = H) and not its 2,3,5-isomer (X). By analogy we assign V and not IV to the tetraester. Furthermore both IV and VII are hemiketals which with acid would undergo ring cleavage to give furan 2,5-dicarboxylic acid.

Structure VI is a possible alternative to V for the tetraester, but spectroscopic data given in Tables 1 and 2 show that the tetraester (and the triester) cannot possess the ethylene oxide structure of VI.

In Table 1 only the bands in the 3500 and 1800–1500 cm^{-1} ranges are given. Below 1500 cm^{-1} and particularly in the 1350–1000 cm^{-1} region the spectra are very complex and it is difficult to distinguish between the C—O stretching absorptions of alcohols and esters.

[1] W. Cocker, W. J. Davis, T. B. H. McMurry and P. A. Start, *Tetrahedron* **7**, 299 (1959).
[2] H. Sutter, *Liebigs Ann.* **499**, 56 (1932).
[3] T. Reichstein, A. Grussner, K. Schindler and E. Hardmeyer, *Helv. Chim. Acta* **16**, 276 (1933).
[4] A. P. Dunlop and C. D. Hurd, *J. Org. Chem.* **15**, 1160 (1950).
[5] A. R. Katritsky and J. M. Lagowski, *Heterocyclic Chemistry* p. 154. Methuen, London (1960).


I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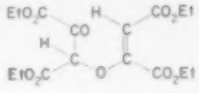
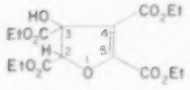
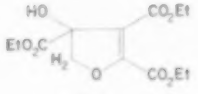

III

IV


V

VI

VII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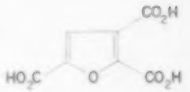
IX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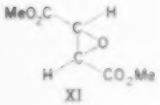

XI

XII

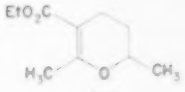

XIII

TABLE 1. INFRA-RED MEASUREMENTS WERE MADE IN NUJOL (n), LIQUID FILM (l) OR CHLOROFORM (c)

Compound	ν_{max} cm^{-1}
Tetraester (V)(n)	3500, 1776, 1764, 1703, 1670, 1650
Triester (VIII)(n)	3500, 1764, 1703, 1650
Furan tetracarboxylic ester (I; R = Me) (n)	1766, 1759, 1747, 1728, 1612
Furan 2,3,4-tricarboxylic ester (IX; R = Me) (n)	1742, 1595m 1545
Methyl furan-3-carboxylate (c)	1726, 1703, 1594, 1581, 1506
trans 1,2-Dimethoxycarbonyl ethylene oxide (XI) (n)[6]	1745
Ethyl β-ethoxyacrylate (XII; R = R^{1} = H; R^{11} = CO_2Et) (l)	1724, 1708, 1652, 1632
Ethyl β-ethoxycrotonate (XII; R = CH_3; R^{1} = H; R^{11} = CO_2Et) (l)	1742, 1650
Ethyl 2,6-dimethyl-2,3-dihydropyran-5-carboxylate (XIII)[7]	1627
Diethyl maleate (l)	1724, 1639
Dimethyl maleate (l)	1724, 1653
Diethyl fumarate (l)	1724, 1647

[6] R. Kuhn and F. Ebel, *Ber. Dtsch. Chem. Ges.* **58**, 919 (1925).
[7] F. E. Bader, *Helv. Chim. Acta* **36**, 215 (1953).

TABLE 2. ULTRA-VIOLET LIGHT ABSORPTION MEASUREMENTS WERE MADE IN ETHANOL

Substance	λ_{max} Å	log ε
Tetraester (V)	2470	3·89
Triester (VIII)	2470	3·88
Furan tetracarboxylic ester (I; R = Me)	2580	4·09
Furan tricarboxylic ester (IX; R = Me)	2450	4·05
trans 1,2-Dimethoxycarbonyl ethylene oxide (XI)	No max	log ε 2·09 at 2300 Å
Ethyl β-ethoxyacrylate (XII; R = R^1 = H; R^{11} = CO_2Et)	2330	4·29
Ethyl β-ethoxycrotonate (XII; R = CH_3; R^1 = H; R^{11} = CO_2Et)	2380	4·09
Diethyl ethoxymethylenesuccinate (XII; R = H; R^1 = CO_2Et; R^{11} = CH_2CO_2Et)	2380	4·02
Ethyl 2,6-dimethyl-2,3-dihydropyran-5-carboxylate (XIII)	2480	4·1
Ethyl oxaloacetate	2650	3·54
Ethyl acetoacetate	2460	3·28
Diethyl maleate	Inf. at 2500	2·95

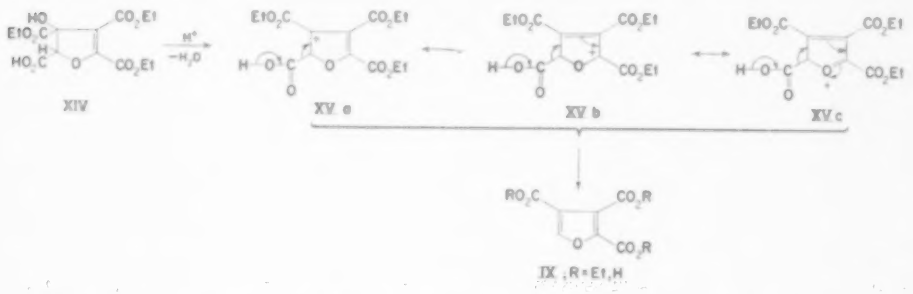
The carbonyl bands at 1776 and 1764 cm^{-1} shown by V and at 1764 cm^{-1} shown by VIII though at unusually high wave numbers are probably due to the unconjugated ester groups, although furan tetracarboxylic ester shows bands at 1766 and 1759 cm^{-1}. The bands at 1703 cm^{-1} are due to conjugated ester groups and similar bands are found at 1724 cm^{-1} in most of the conjugated esters listed. The strong bands at 1650 cm^{-1} shown by V and VIII are undoubtedly associated with conjugated C=C. Similar bands are found at 1632–1653 cm^{-1} in the unsaturated esters listed in Table 1. *trans* 1,2-Dimethoxycarbonyl ethylene oxide (XI) which lacks the ethylenic double bond but contains an oxide structure similar to that of VI shows no absorption save that of the ester groups.

The ultra-violet data emphasize the similarity of V and VIII, though it will be noticed that both absorb maximally at 100 to 200 Å higher than the analogous acyclic unsaturated esters. The bathochromic effect is presumably a function of the ring system, and this suggestion finds support in a comparison of the maximum exhibited by ethyl 2,6-dimethyl-2,3-dihydropyran-5-carboxylate (XIII) and its acyclic analogue ethyl β-ethoxycrotonate (XII; R = CH_3; R^1 = H; R^{11} = CO_2Et). The intensity of the maximum absorption of V and VIII is similar to that exhibited by the esters bearing the group RO_2C—C(R)=C(R)OR and is uniformly greater by an order of magnitude than the intensity shown by diethyl maleate which lacks the vinyl ether function. The spectrum of *trans* 1,2-dimethoxycarbonylethylene oxide (XI) shows that the ethylene oxide ring (present in VI) does not behave like an α,β-unsaturated ester or a cyclopropane ring conjugated with an ester group.

The nuclear magnetic resonance spectrum of V also supports its structure. It shows a peak at 4·88 p.p.m. due to a single hydrogen α- to the ether oxygen and to the ester carbonyl. The single hydrogen in IV would be expected to show a peak at 7·5 p.p.m. The methylene groups of the ethyl groups give a complex series of bands

around 5·69 p.p.m. A peak at 5·99 p.p.m. is due to the hydroxyl hydrogen. The combined weight of these peaks corresponds to 9 hydrogens. The complex bands around 8·66 p.p.m. are due to the 12 hydrogens of the 4 methyl groups.

When either V or VIII is refluxed with hydrochloric acid, furan-2,3,4-tricarboxylic acid (IX; R; H) is obtained, in the former case admixed with the tetracarboxylic acid. Since furan tetracarboxylic acid, (I; R = H), is unaffected by treatment with hydrochloric acid, the decarboxylation of V must occur before the furan ring is formed. We believe that the secondary 2-ethoxycarbonyl group is the most readily hydrolysed of the four, thus giving XIV, but whether the decarboxylation takes place before or after hydrolysis of the remaining three ester groups is immaterial. The actual decarboxylation is probably preceded by protonation of the 4-hydroxyl group, followed by loss of water, to afford the intermediate XV to which the three canonical forms XVa, XVb and XVc contribute. The intermediate will readily lose a proton and carbon dioxide to afford furan 2,3,4-tricarboxylic acid (IX). A rather similar mechanism has been advanced for the acid catalysed decarboxylation of cinnamic acids.[8]



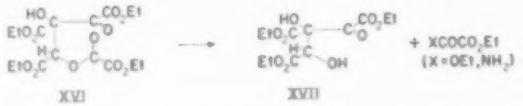
Since V is prepared under basic conditions the epimerizable centre at C_2 will adjust itself so that the 2- and 3-ethoxycarbonyl groups become *trans* with respect to each other. The loss of water to give furan tetracarboxylic ester (I; R = Et) when V is treated with concentrated sulphuric acid is thus explained. We have also shown that the dehydration can be effected using a mixture of acetic anhydride and pyridine, though dehydration with phosphorus oxychloride and pyridine, or with acetyl chloride or thionyl chloride was not possible.

We were unable to reduce the tetraester V by catalytic methods or by the use of zinc in ethanol, zinc in acetic acid, or the latter reagent containing silver nitrate.[9] Bromination of V could not be effected but a model of V, using space-filling models, shows that the 4- and 5-ester groups are very close together, and that access by bromine to the double bond must be very difficult.

Ozonolysis of V in ethyl acetate afforded a viscous product which gave no ferric reaction. The product showed a maximum at 3500 cm^{-1} in the infra-red, but the peak at 1650 cm^{-1} (C=C) shown by V had disappeared, and a broad band at 1745 cm^{-1} (carbonyl) appeared in place of the four carbonyl peaks exhibited by V. The ozonolysis product reacted rapidly with ammonia to give one molecule of oxamide for molecule of V, and with ethanol it afforded ethyl oxalate. These properties are consistent with an ozonolysis product of structure XVI, but attempts to isolate a

[8] W. S. Johnson and W. E. Heinz, *J. Amer. Chem. Soc.* **71**, 2913 (1949).
[9] P. Bladon, *J. Chem. Soc.* 2176 (1955).

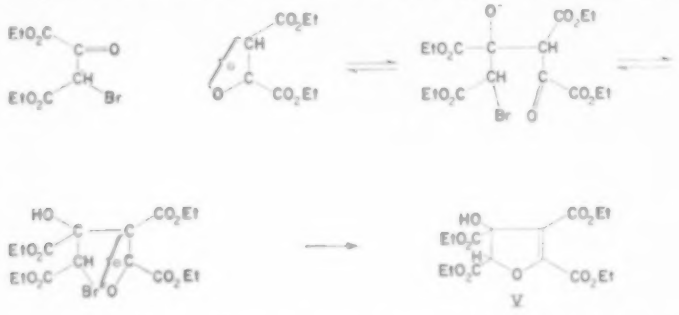
compound of structure XVII from XVI failed. The ozonolysis product of IV would give a ferric reaction.



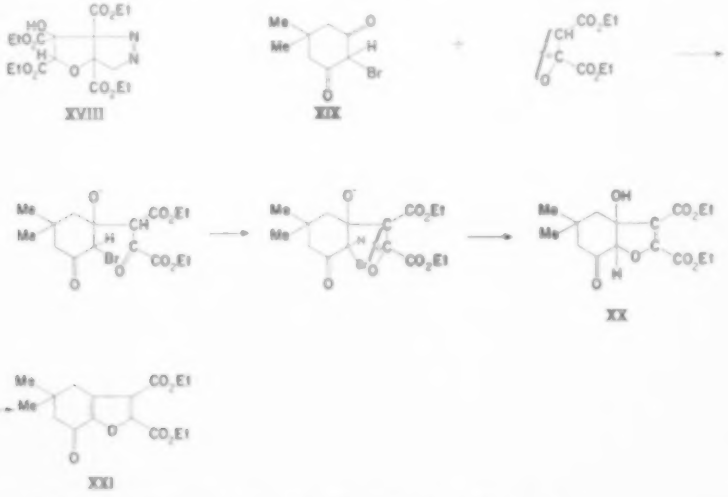
XVI XVII

Diazomethane reacted only very slowly with the tetraester (V), to give a viscous liquid which was no longer unsaturated, but it possessed a band at 1540 cm^{-1} in the infra-red which can be assigned to an imidazoline C=N or N=N (cf. XVIII).

We envisage the formation of the tetraester (V) by the reaction sequence shown below.



Whilst in the case of the simple ketones the equilibrium of the first stage of the reaction lies to the left[10] the effect of the bromine atom and the carbethoxy groups will be to increase the activity of the carbonyl group. In this connection we should mention that all our attempts to condense ethyl α-bromoacetoacetate with ethyl sodioacetoacetate failed, even when pyridine was used as a solvent. The difference in reactivity between ethyl bromo-oxaloacetate or ethyl bromopyruvate and ethyl bromoacetoacetate is readily explained by the greater reactivity of the keto group in the first two compounds, flanked as it is by —CO_2Et and —CHBr-groups.



XVIII XIX XX XXI

[10] J. Hine, *Physical Organic Chemistry* p. 253. McGraw-Hill, New York (1956).

Attempts were also made to condense bromodimedone (XIX) with ethyl sodio-oxaloacetate according to the following reaction sequence—XIX → XX → XXI, but the only product was the tetraester (V) in high yield.

Bromodimedone must thus act as a brominating agent converting part of the ethyl sodio-oxaloacetate to ethyl bromo-oxaloacetate. No reaction occurred when sodiodimedone was shaken with ethyl bromo-oxaloacetate or bromodimedone. This may be due to steric factors, or, as is more likely, to the stability of the enolate of the dimedone.

When ethyl γ-bromoacetoacetate was reacted with ethyl sodio-oxaloacetate, the bromo ester condensed with itself, the product being ethyl succinylsuccinate. This compound has been prepared by the self-condensation of ethyl γ-haloacetoacetates in the presence of bases.[11] Ethyl sodio-oxaloacetate can obviously supply the base.

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EXPERIMENTAL

Ethyl α-bromo-oxaloacetate was prepared by the method of Conover and Tarbell[12].

Reaction of ethyl α-bromo-oxaloacetate with ethyl oxaloacetate

(a) *With ethyl sodio-oxaloacetate.* Finely powdered ethyl sodio-oxaloacetate (6 g) was added to a solution of ethyl α-bromo-oxaloacetate (5 g) in ether (50 cc) and the mixture was shaken for several hours and then set aside overnight. The mixture was filtered and the ethereal filtrate evaporated to dryness. The residue was washed with ice-cold ether giving tetraethyl 2,3-dihydro-3-hydroxyfuran-tetracarboxylate (V, 2·1 g; 30%), m.p. 82–83° undepressed by an authentic specimen.

(b) *With pyridine as catalyst.* A mixture of ethyl α-bromo-oxaloacetate (5 g) and ethyl oxaloacetate (5 g) in ether (10 cc) was treated with freshly distilled and dried pyridine (2 cc), and set aside overnight. The mixture was filtered and the ethereal filtrate washed with dil H_2SO_4 and then with water. The residue on evaporation of the ether was a yellow oil which slowly crystallized giving V. On washing with ice-cold ether it was obtained as colourless needles (0·25 g), m.p. 80–83°, undepressed by an authentic specimen.

Tetraethyl furantetracarboxylate (I; R = Et)

A mixture of tetraethyl 2,3-dihydro-3-hydroxyfurantetracarboxylate (V) (2 g), acetic anhydride (5 cc) and pyridine (5 cc) was heated on a water bath for 2 hr. The mixture was poured into ice-water (30 cc) and neutralized with sodium carbonate. The solution was extracted with ether, and the ether layer washed with N H_2SO_4 and water and dried (Na_2SO_4). The product was chromatographed on neutral alumina (Woelm brand, 30 g). Elution with benzene–light petroleum (b.p. 40°–60°) gave tetraethyl furantetracarboxylate (I; R = Et; 0·4 g), m.p. and mixed m.p. 34°.

Reaction of bromodimedone with ethyl sodio-oxaloacetate

Bromodimedone was prepared as follows.[13] A stirred mixture of dimedone (10 g) sodium acetate (6·3 g) and glacial acetic acid (100 cc) was slowly treated with bromine (4 cc) in glacial acetic acid (70 cc). After stirring for a further 1 hr, water (600 cc) was added and the deposited solid collected and washed free from bromide. After drying in a desiccator it weighed 11·5 g, m.p. 173–174°.

Bromodimedone (2 g) was added to a suspension of ethyl sodio-oxaloacetate (3 g) in ether (50 cc) and the mixture was shaken for 20 hr. The mixture was filtered and the filtrate freed from ether giving a lachrymatory oil from which the tetra ester (V, 1·5 g), m.p. and mixed m.p. 82–83° was deposited. The lachrymatory oil smelled strongly of ethyl α-bromo-oxaloacetate.

Ozonolysis of the tetraester (V)

A solution of the tetraester (5 g) in ethyl acetate (100 cc) cooled in solid CO_2, was treated with ozonized oxygen for 8·5 hr, when it was no longer absorbed. The ozonide was then hydrogenated

[11] W. Mewes, *Liebigs Ann.* **245**, 58 (1888); R. Schonbrodt, *Ibid.* **253**, 168 (1889).
[12] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.* **72**, 5221 (1950).
[13] T. Voitila, *Chem. Abstr.* **33**, 7742 (1939).

over palladized charcoal giving a viscous liquid which was diluted to 15 cc with ethanol. (A). This solution (2 cc) was treated with an excess of ammonia (5 cc, *d*, 0·880). Considerable heat was evolved and a deep violet solution was obtained from which oxamide (0·2 g) was deposited. (B). Anhydrous hydrogen chloride was passed into the ethanolic solution (13 cc) for 2 min, the solution was then refluxed for 0·5 hr, and the ethanol was removed. The residue was dissolved in chloroform, washed several times with water, dried and distilled giving ethyl oxalate (0·75 g), b.p. 188°.

Action of diazomethane on the tetraester (V)

The tetraester (500 mg) was dissolved in ether (5 cc) and set aside with an excess of diazomethane in ether for 1 week. The product was an oil, which showed no maximum at 1650 cm^{-1} but a new maximum at 1540 cm^{-1}.

1,4-*Diethyl cyclohexan*-2,5-*dionedicarboxylate* (ethyl succinylsuccinate)

Ethyl γ-bromoacetoacetate[13] (from ethylacetoacetate, 50 g) was shaken for 20 hr with excess ethyl sodio-oxaloacetate in ether. The salts formed were collected at the pump, and the ether removed to afford ethyl succinylsuccinate (4·3 g), as pale yellow needles, m.p. 124–125°, undepressed on admixture with an authentic specimen.[15] (Found: C, 56·6; H, 6·0. Calc. for $C_{14}H_{18}O_7$: C, 56·4; 6·1%). It formed an acetate (acetic anhydride–pyridine), m.p. and m.p. 170°. (Found: C, 56·6; H, 6·0. Calc. for $C_{16}H_{20}O_8$: C, 56·5; H, 5·9%).

Acknowledgements—The authors are grateful to Messrs. A. Boake, Roberts & Co. Ltd., for gifts of ethyl sodio-oxaloacetate and to the Rohm and Haas Co. for samples of ethyl β-ethoxyacrylate and diethyl ethoxymaleate. One of us (I. J. C.) is indebted to the County of Armagh Education Committee and to the Ministry of Education for Northern Ireland for maintenance grants.

We are grateful to Dr. L. M. Jackman for the N.M.R. data.

[14] A. Burger and G. E. Ullyot, *J. Org. Chem.* **12**, 342 (1947.)
[15] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **48**, 772 (1915.)

Tetrahedron, 1961, Vol. 15, pp. 53 to 59. Pergamon Press Ltd. Printed in Northern Ireland

THIOPEGAN DERIVATIVES—XXI

A MECHANISM FOR THE FORMATION OF 9:10 AND 10:11 THIOPEGAN DERIVATIVES

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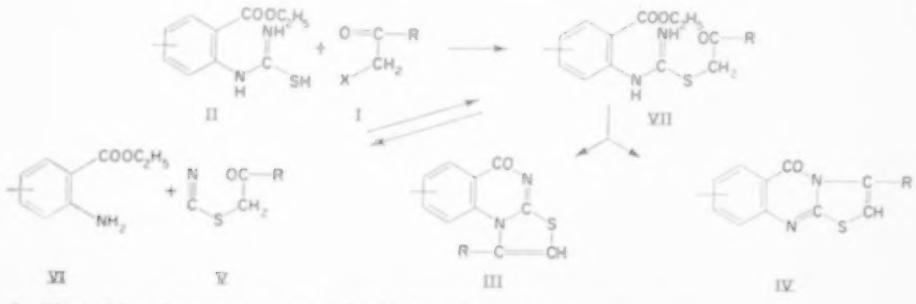
(*Received* 18 *March* 1961)

Abstract—Reactions between α-haloketones and *o*-carbethoxy phenyl thiourea have been discussed; a mechanism for the observed exclusive formation of 9:10-thiopega-2:10-diene-4-ones in the case of α-haloalkaryl ketones has been advanced and a number of intermediates isolated in case of chloro acetone.

NARANG *et al.* have shown that interaction of α-haloketone (I) with *o*-carbethoxy-phenylthiourea (II) in general leads to the formation of 9:10-thiopegan derivatives (III). The only exception observed was that of chloroacetone which in addition to yielding the corresponding 9:10-thiopegan derivatives (III, R = CH_3) gave appreciable amounts of the 10:11-isomer (IV, R = CH_3).[2,3] It was further observed that if this reaction between the haloketones and the thiourea was stopped after a few minutes heating in ethanol, α-thiocyano ketone (V) corresponding to the α-haloketone (I) employed, could be isolated from the reaction mixture while the thiourea (II) was found to have retrograded to anthranilic ester (VI).[1] The authors thus postulated that the first reaction product can be VII which could cyclize to the thiopegan derivatives both with linear (10:11; IV) or angular (9:10; III) annulation. The thiourea adduct (VII) could also account for the observed formation of the α-thiocyanoketones and anthranilic ester as shown; the retrogression being:



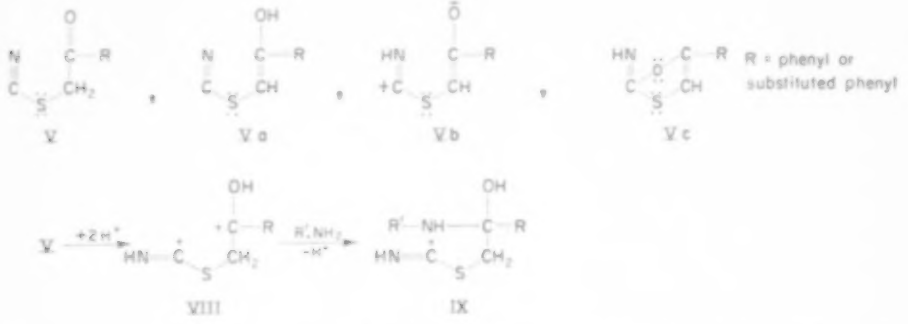
facilitated by the presence of COOH or $COOC_2H_5$ groups.

The above mechanism was further elaborated by these authors[4,5] in view of a

[1] D. S. Bariana, M. S. Dhatt, H. S. Sachdev and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 848 (1954).
[2] G. M. Sharma, I. S. Gupta and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 959 (1955).
[3] H. S. Sachdev and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 427 (1955).
[4] S. Gurjit, H. S. Sachdev and K. S. Narang, *J. Sci. Ind. Res.* **16B**, 359 (1957).
[5] H. S. Sachdev, K. S. Dhami and K. S. Narang, *J. Sci. Ind. Res.* **19C**, 11 (1960).

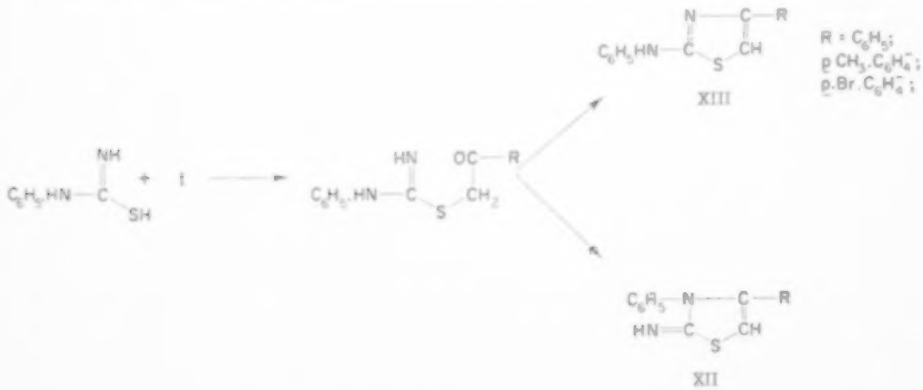
subsequent finding that the same 9:10-thiopegan derivatives (III) could be obtained in the same facile manner by the interaction of α-thiocyanoalkaryl ketones (corresponding to the α-haloalkarylketones previously used) and anthranilic acid or ester in presence of acid catalysts. This mechanism, however, again visualized the thiourea adduct VII as being the precursor for the formation of 9:10-thiopegans.[4]

It is considered likely that α-thiocyanoalkarylketones which can exist in various tautomeric forms V, Va, Vb, Vc could react with an amino group in two ways depending upon whether the C of the carbonyl group or that of the thiocyano group is first attacked. The former course shall give rise to an intermediate (IX) which will exclusively lead to the formation of 9:10-thiopegans (*vide infra*) while the latter would give

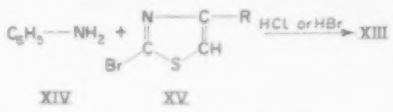


rise to the thiourea adduct (VII) which now could afford both varieties of the thiopegans.

Therefore, to further understand the mechanism of thiopegan formation it was considered desirable to study the reaction between an α-haloketone and a substituted thiourea where the factors leading to the retrogression of the intermediate adduct were precluded. Consequently a few condensations between phenylthiourea and some α-haloalkarylketones have been carried out. The intermediate adduct (X) which could again be considered capable of giving two types of products XII and XIII would not be expected to retrograde because of the absence of carboxy or carbethoxy groups on its N-phenyl part. In these reactions, only one type of product could be isolated for which 2-anilino-4-arylthiazole structure (XIII) has been confirmed through an



unambiguous synthetic route involving the interaction of aniline (XIV) with a requisite 2-bromo-4-arylthiazoles (XV) as shown:

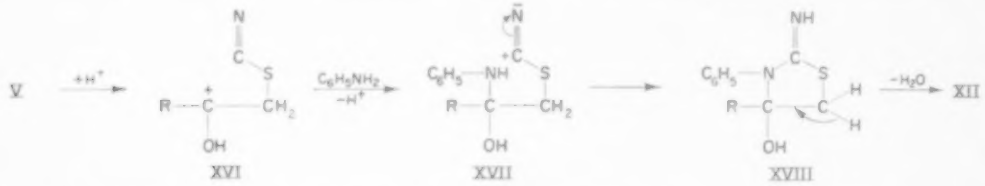


XIV XV

Excellent yields of the thiazole derivatives (XIII) were realized by carrying out these condensations in phenol solution in presence of catalytic amounts of hydrobromic acid or hydrochloric acid in contrast to the basic catalysts employed by some previous workers who recorded lower yields.[6–8]

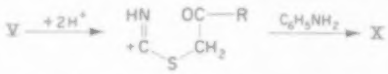
However, when α-thiocyanoalkarylketones corresponding to the α-haloalkarylketones, employed in the above set of condensations, were reacted with aniline in presence of mineral acid catalyst, a different series of thiazole derivatives were obtained to which the 2-amino-thiazoline-4-structure (XII) can be assigned with a reasonable certainty. The mechanistic trend of the reaction can be depicted as under:

An alternative reaction course visualizing an initial nucleophilic attack at the C



XVI XVII XVIII

of the thiocyano group as shown below, is discounted as that would give rise to the thiourea intermediate (X) which should furnish XII as well as XIII but only one product (XIII) has been isolated from the cyclization of the thiourea (X).



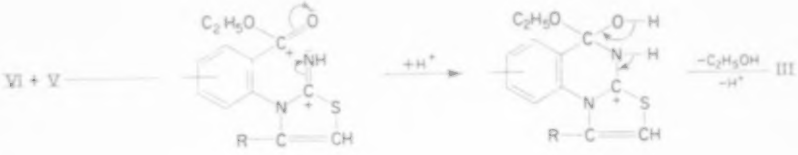
In the above reaction if the addition of one H^+ to V could be assumed to take place in the initial stage, it should preferably add to C=O with the formation of XVI and if addition of 2H could be presumed leading to the formation of VIII it is evident that the electrophilic activity on $-C^+-$ is stronger than on $-S-C^+=NH$; presence

of sulphur with unshared electrons possibly reduces the electrophilicity of carbon in $S-C^+=NH$.

In none of these reactions the formation of two products could be detected. The 2-imino-thiazolines-4 (XII) and 1-anilino-4-arylthiazoles (XIII) could be regarded as prototypes of 9:10-(III) and 10:11-(IV) thiopegans respectively. The foregoing observations suggest that the reaction between *o*-carbethoxyphenylthiourea (II) and α-haloalkarylketones (I) is equivalent to that between an α-thiocyanoalkarylketone and anthranilic ester and apparently in the former case the intermediate adduct (VII) undergoes complete retrogression to the products of the latter reaction, which then

[6] I. A. Kaye and C. L. Parris, *J. Amer. Chem. Soc.* **74**, 6921 (1952).
[7] J. N. Ashley and J. F. Grove, *J. Amer. Chem. Soc.* **67**, 768 (1945).
[8] Elderfield, *Heterocyclic Compounds* Vol. V, p. 610. John Wiley, New York (1957).

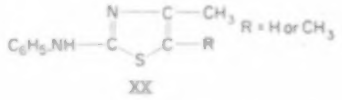
interact in a manner similar to that of the reaction between aniline and α-thiocyanoketones. An imino-thiazoline-4-derivative (XIX) would be expected to be the precursor of the 9:10-thiopegans (III) as indicated (first few steps similar to these in structures (XVI–XVIII) have been omitted).



XIX

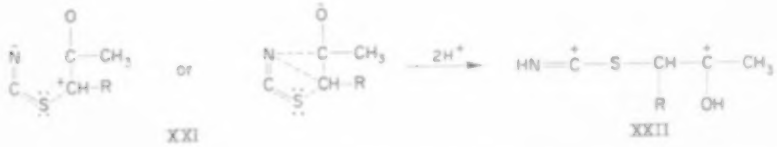
From the foregoing it could be concluded that in the formation of linear thiopegans, the precursor would essentially be thiourea derivatives of the type X while the angular thiopegans are formed from the intermediates of the type XVII.

There seems to be a divergence from the above generalization in the case of aliphatic α-thiocyanoketones. Both the thiocyanoacetone and α-thiocyanoethylmethyl-ketone exclusively give 2-anilinothiazoles (XX) and not the corresponding 2-iminothiazolines, when reacted with aniline in the presence or absence of protonic reagents, the reaction is, however, slow in the absence of protonic catalysts. The identity of 2-anilino-4-methylthiazole and 2-anilino-4:5-dimethylthiazole[10] has been confirmed through their unambiguous syntheses involving the reaction between aniline and corresponding 2-chlorothiazoles. Since the thiocyanoacetone and α-



XX

thiocyanoethylmethyl-ketone give only 2-anilinothiazoles, it indicates that aliphatic α-thiocyanoketones can, partly acquire structure XXI in addition to those already postulated for the α-thiocyanoacetophenones.

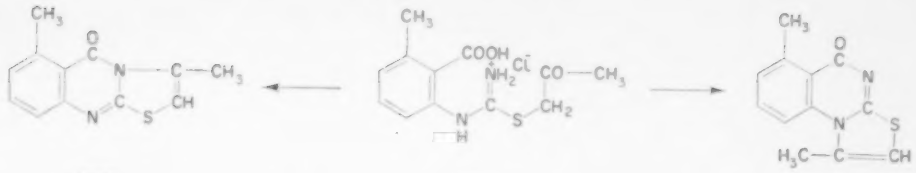


XXI XXII

It is, evident that in the structure XXII which XXI acquires by taking two H^+, it is the —S—C^+=NH, which reacts with the amino group while the C of the carbonyl is lacking the requisite + ve charge to undergo such reaction.

Again when, reviving the reactions between thiocyanoacetone and various anthranilic acids, it was possible in the case of 6-methylanthranilic acid, to isolate and purify the intermediate (XXIII), which furnishes 9:10-thiopegan (XXIV) on dry heating and 10:11-thiopegan (XXV) on refluxing in alcohol.

[9] W. Traube, *Ber. Dtsch. Chem. bes.* **32**, 3156 (1899).
[10] R. A. Mathes, *J. Amer. Chem. Soc.* **74**, 1719 (1952).



XXV XXIII XXIV

The intermediate (XXIII) is assigned the thioureanium salt structure on the basis of its elemental analysis and its flexibility to cyclize in either fashion under two different sets of conditions.

Further work on various aspects of the mechanism of the reactions involved and the peculiar behaviour of the aliphatic and aromatic thiocyano ketone is in hand.

EXPERIMENTAL

Condensation of phenyl thiourea with ω-bromoacetophenones

Formation of 2-anilino-4-aryl thiazoles (XIII). Equivalent quantities of the requisite ω-bromoacetophenone and phenylthiourea, dissolved in minimum amount of absolute ethanol were refluxed for 4–5 hr on a water bath with separation of a white solid. The solvent was removed under red. press. and the residue basified with sodium hydroxide, washed with water and crystallized from a suitable solvent (Table 1).

Interaction of 2-bromo-4-arylthiazoles with aniline hydrobromide

Direct synthesis of 2-anilino-4-aryl thiazoles (XIII). 2-Bromo-4-arylthiazoles were obtained from the corresponding α-thiocyanoketones by treatment with dry hydrobromic acid gas.[11,12]

Equivalent amounts of the requisite 2-bromo-4-arylthiazoles and aniline hydrobromide were taken in phenol (2 ml per gramme of the reactant) and heated in an oil bath at 130–140° for about 6–7 hr. After this the reaction mixture was cooled and basified with sodium hydroxide to remove phenol and washed with water. The solid product was crystallized from a suitable solvent (Table 1). The identity of these products was confirmed by mixed m.p. determination with the corresponding products obtained above.

Interaction of ω-thiocyanoacetophenones with aniline hydrobromide

Synthesis of 2-imino-3-phenyl-4-substituted phenylthiazoles (XII). Equimolecular amounts of the requisite ω-thiocyanoacetophenone and aniline hydrobromide were dissolved in a minimum amount of dry ethanol and the mixture heated under reflux for 5–6 hr with separation of a white solid. The solvent was removed by distillation on a water bath and the residue basified with sodium hydroxide, washed with water and crystallized from suitable solvent (Table 2).

In the case of 2-imino-3,4-diphenyl- and 2-imino-3-phenyl-4-bromophenyl-thiazoline-4, their hydrobromides were also isolated which were analysed after crystallization from glacial acetic acid (Table II).

R = H (XX). A solution of aniline hydrochloride (1·3 g; 1·0 mole) in absolute alcohol (15 ml) was added to thiocyanoacetone (1·2 g; 1·0 mole) taken in the same solvent. After keeping the mixture at room temp. for 20 hr it was basified with sodium hydroxide solution. The product was crystallized from ethanol, m.p. 117°; yield 0·8 g (42·1%) and confirmed as 2-anilino 4-methyl-thiazole.[9]

R = CH_3 (XX). 2-Chloro-4:5-dimethyl thiazole[13] (1·5 g; 1·0 mole) was mixed with aniline hydrochloride (1·3 g; 1 mole) and phenol (7 ml). The mixture was heated at 130–140° for 2 hr, cooled, basified with 2% sodium hydroxide and the residual solid crystallized from dil. ethanol, m.p. 105°, yield 1·5 g. It was identical with the product obtained by Mathes[10] by the interaction of α-thiocyanoethylmethylketone and aniline hydrochloride.

[11] D. S. Bariana, H. S. Sachdev and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 427 (1955).
[12] N. K. Ralhan, K. Gurmit, H. S. Sachdev and K. S. Narang, In press.
[13] K. Ganpathi and A. Venkataraman, *Proc. Ind. Acad. Sci.* **32**, 374 (1945).
[14] H. S. Sachdev, N. K. Ralhan, M. S. Atwal, H. S. Garg and K. S. Narang, *J. Sci. Ind. Res.* **19B**, 217 (1960).

TABLE 1. 2-ANILINO-4-ARYL THIAZOLES (XIII)*

S. No.	Reactants	Product	Solvent of crystallization	Yield %	m.p. and mixed m.p.	M.F.	Analysis Found %	Analysis Required %
1a	Phenylthiourea and ω-bromoacetophenone	2-anilino-4-phenylthiazole	pet ether (80°–100°)	70	136°	$C_{15}H_{12}N_2S$	N, 11·6	N, 11·11
1b	Aniline hydrochlofide and 2-bromo-4-phenylthiazole	2-anilino-4-phenylthiazole	pet ether (80°–100°)	60	136°			
2a	Phenyl thiourea and ω-bromo-*p*-methylacetophenone	2-anilino-4-(*p*-tolyl)thiazole	pet ether (80°–100°)	72	92–100°	$C_{16}H_{14}N_2S$	N, 10·10	N, 10·52
2b	Aniline hydrobromide and 2-bromo-4-(*p*-tolyl)thiazole	2-anilino-4-(*p*-tolyl)thiazole	pet ether (80°–100°)	67	92–100°			
3a	Phenylthiourea and ω-*p*-dibromoacetophenone	2-anilino-4-(*p*-bromophenyl)thiazole	pet ether (80°–100°)	65	145°	$C_{15}H_{10}N_2SBr$	C, 54·50 H, 3·33 N, 8·5	C, 43·38 H, 3·32 N, 8·45
3b	Aniline hydrobromide and 2-bromo-4-(*p*-bromophenyl)thiazole	2-anilino-4-(*p*-bromophenyl)thiazole	pet ether (80°–100°)	66	145°			

* Note: Table 1 hydrobromides of S. No. 1, 2 and 3 have m.p. 185°, 209° and 218° respectively and crystallize from g. acetic acid.

TABLE 2. 2-IMINO-3-PHENYL-4-SUBSTITUTED PHENYL THIAZOLINE-4 (XII)

S. No.	Reactants	Product	Solvent of crystallization	Yield %	m.p. and mixed m.p.	M.F.	Analysis Found %	Analysis Required %
1.	Aniline hydrobromide and ω-thiocyanoacetophenone	2-amino-3:4-diphenyl-thiazoline-4 (hydro-bromide	glacial acetic acid	71	300°	$C_{15}H_{13}N_2SBr$	N, 7·9	N, 8·4
		base)	pet-ether (80–100°)	84	84°	$C_{15}H_{12}N_2S$	C, 71·23 H, 5·05 N, 10·77	C, 71·42 H, 4·78 N, 11·11
2.	Aniline hydrobromide ω-thiocyano *p*-methyl-acetophenone	2-imino-3-phenyl-4-(*p*-tolyl)thiazoline-4 (hydrobromide	glacial acetic acid	61	309°			
		base)	pet-ether (80–100°)	93		$C_{16}H_{14}N_2S$	N, 10·29	N, 10·53
3.	Aniline hydrobromide ω-thiocyano-*p*-bromo-phenylacetophenone	2-imino-3-phenyl-4-2-bromophenyl-thiazolin-4 (hydro-bromide	glacial acetic acid	84	377°	$C_{15}H_{12}N_2SBr$	Br, 39·07	Br, 38·83
		base)	pet-ether (80–100°)		122°			

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(b) A mixture of α-thiocyanoethylmethylketone (1·3 g) and aniline (0·9 g) in absolute ethanol (25 ml) after refluxing for 8 hr furnished 0·8 g of XX (R = CH_3).

Isolation of XXIII. Thiocyanoacetone (0·57 g; 1·0 mole) taken in absolute ethanol (5 ml) was added to a solution of 6-methylanthranilic acid hydrochloride (0·9 g, 1·0 mole) in the same solvent (15 ml). In about 10 min at room temp. fine needles separated. The product was collected and repeatedly washed with absolute ethanol, yield 0·75 g. This product first melts at 187°, solidifies and again melts at 247°. It could not be recrystallized and a sample prepared from very pure raw materials was analysed. (Found: C, 49·46; H, 4·45; N, 9·25; S, 11·0; Cl, 11·74 $C_{12}H_{15}O_3N_2SCl$ requires: C, 49·60; H, 4·96; N, 9·26; S, 10·6; Cl, 11·73%).

XXV. A mixture of 2-chloro-4-methyl thiazole (0·67 g, 1·0 mole) and 6-methylanthanilic acid (0·75 g; 1·0 mole) in phenol (5 ml) was heated in an oil bath, the temperature of which was raised to 180° during half an hour. It was further heated for 2 hr cooled and basified with sodium hydroxide solution. The solid collected, washed free of alkali and crystallized from ethanol as white needles m.p. 225°, yield 0·45 g (41%).

Formation of XXV *from* XXIII. The intermediate XXVII (R = H, R_1 = CH_3) on refluxing in alcohol for about 6 hr and subsequent removal of the solvent furnish a compound, m.p. 225° which is identical with the product obtained above.

Formation of XXV *from* XXIII. The intermediate was heated in an oil bath at 180–190° for about 2 hr and then crystallized from ethanol as white needles, m.p. 247. (Found: S, 13·76; N, 12·20; $C_{12}H_{10}N_2OS$ requires: S, 13·91; N, 12·20%).

Tetrahedron, 1961, Vol. 15, pp. 60 to 65. Pergamon Press Ltd. Printed in Northern Ireland

APPLICATION OF THE BRUCKNER METHOD TO THE SYNTHESIS OF PHENANTHRIDINES—IV[1]

STRUCTURE OF THE SO-CALLED NITROSITES FROM THE ADDITION OF DINITROGEN TRIOXIDE TO 1-ARYLCYCLOHEXENES

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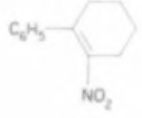
(*Received* 20 *March* 1961)

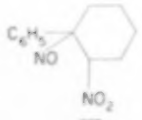
Abstract—The solid byproducts formed in the addition of dinitrogen trioxide to 1-arylcyclohexenes have been shown to be 3-nitro-2-aryl-2-cyclohexenone oximes arising from nitrosation of 2-nitro-1-arylcyclohexenes.

THE first paper[2] of this series reported the formation of a yellow solid, m.p. 224° (decomp) by the reaction of 1-phenylcyclohexene (I) with dinitrogen trioxide under certain conditions. Under other conditions, the predominant product was 2-nitro-1-phenylcyclohexene (II). The solid dissolved in cold alcoholic alkali, yielding a deep red solution, from which it was recovered unchanged by acidification. It afforded an acetate with acetic anhydride in pyridine, from which again it was regenerated by mild hydrolysis. Oxidation of the yellow solid gave a good yield of benzoic acid. These data and preliminary analytical results on the solid led to the tentative formulation[2] of its structure as 2-nitro-1-nitroso-1-phenylcyclohexane (III). Analogous

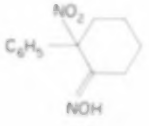
I



II



III



IV

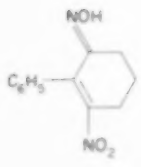
compounds were obtained from the addition of dinitrogen trioxide to 1-*o*, 1-*m* and 1-*p*-tolyl and 1-*m*-methoxyphenylcyclohexenes.[2] However structure III was not entirely compatible with the properties observed for the yellow solid, m.p. 224° (decomp). Further investigations leading to a revision of the tentative formulation are reported in this paper.

A plausible alternate structure IV suggested by Prof. D. H. R. Barton[3] would also explain the properties of the yellow solid. The oxime IV would presumably arise by rearrangement of the intermediate normal nitrosite III[3] and isomerization of the

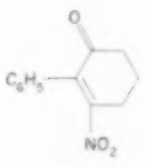
[1] Part III, T. R. Govindachari, K. Nagarajan, B. R. Pai and V. N. Sundararajan, *Chem. Ber.* **91** 2053 (1958).
[2] T. R. Govindachari, K. Nagarajan, B. R. Pai and N. Arumugam, *J. Chem. Soc.* 4280 (1956).
[3] We are thankful to Prof. Barton, Imperial College of Technology, London, for his suggestion.

secondary nitroso compound to the oxime. The compound indeed contained one active hydrogen and its I.R. spectrum showed, in addition to the bands at 1344 and 1508 cm^{-1} characteristic of the nitro group, a band at 3226 cm^{-1} indicative of the presence of a hydroxyl group. The compound was shown to be an oxime by acid hydrolysis to a crystalline ketone, m.p. 109–110° from which it could be regenerated in quantitative yield by treatment with hydroxylamine in pyridine solution. The ketone was further characterized as its semicarbazone and 2,4-dinitrophenylhydrazone. However the I.R. spectrum of the ketone ($\nu_{C=O}$ 1685, $\nu_{C=C}$ 1645 cm^{-1}) and the U.V. spectrum of its 2,4-dinitrophenylhydrazone (λ_{max} 380 mμ)[4] were consistent with an α,β-unsaturated cyclohexanone structure, rather than with the saturated cyclohexanone corresponding to IV. Results of repeated, careful analysis of the ketone, its oxime and other derivatives were in definite agreement with the molecular formula of $C_{12}H_{11}NO_3$ for the ketone and $C_{12}H_{12}N_2O_3$ for the oxime, supporting the presence of a double bond, inferred from spectral evidence. The N.M.R. spectrum of the ketone[5] showed the double bond to be tetrasubstituted, since peaks were observed only in the phenyl and ring methylene regions with an intensity ratio of 5:6. The peaks due to the methylene groups were resolved into three groups of equal area and the line positions of two of these groups were in the allylic region.

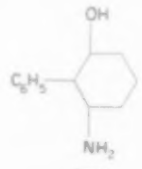
Reduction of the ketone with sodium borohydride afforded a mixture of products from which a small amount of a neutral crystalline alcohol, $C_{12}H_{15}NO_3$ was obtained. Reduction of both the carbonyl group and the double bond must have taken place.[6] Lithium aluminium hydride reduction yielded a mixture of oily amines, separated by fractional crystallization of the hydrochlorides. Two isomeric crystalline hydrochlorides, $C_{12}H_{18}ClNO$, m.p. 327–330° (decomp) and m.p. 241° respectively, were thus obtained and both were found to be resistant to cleavage by sodium metaperiodate, indicating the absence of a vicinal 1,2-aminoalcohol system. The evidence cited so far would be consistent only with structure VII for the amino alcohols,[7] thus leading to structures VI and V for the ketone and the 'yellow solid' oxime, respectively.



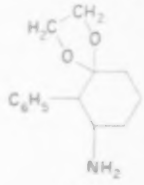
V



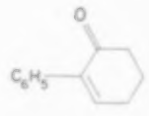
VI



VII



VIII



IX

[4] The presence of a nitro group adjacent to the carbonyl group in the ketone from IV may be expected to have an effect on the U.V. maximum of its 2,4-dinitrophenylhydrazone. However for a model compound, 2-nitroacetone 2,4-dinitrophenylhydrazone (λ_{max} 350 mμ), this effect was shown to be hypsochromic rather than bathochromic.

[5] We are grateful to Prof. J. D. Roberts, California Institute of Technology, Pasadena, for the use of the N.M.R. spectrometer.

[6] cf. D. H. R. Barton, P. deMayo and M. Shafiq, *J. Chem. Soc.* 929 (1957).

[7] The stereochemistry of these compounds has not yet been studied.

Further proof was obtained by the following alternate sequence of reactions: the ketone VI was converted into its ethylene ketal which was then reduced to the amino-ketal VIII.[7] Attempted hydrolysis of VIII with hot 4 N hydrochloric acid led to the formation of a neutral ketone identified as 2-phenyl-2-cyclohexenone (IX). Evidently ketal cleavage is accompanied by elimination of the elements of ammonia from the resultant β-aminoketone system.[8] The 1,3-disposition of nitro and carbonyl groups in the ketone VI was thus further substantiated. In analogy with V, the solids obtained from the addition of dinitrogen trioxide to other 1-arylcyclohexenes must be formulated as 2-aryl-3-nitro-2-cyclohexenone oximes and the ketones derived therefrom as 2-aryl-3-nitro-2-cyclohexenones.

The reaction of dinitrogen trioxide with 1-phenylcyclohexene presumably gives an unstable nitrosite which decomposes to give 2-nitro-1-phenylcyclohexene (II). Oxime V may be formed by nitrosation of the reactive methylene group at position 6 in II. Treatment of an ethereal solution of II with dinitrogen trioxide did not yield V; thus in the experimental procedure described previously,[2] the oxime V was not formed prior to but during the sodium methoxide treatment employed for separating the neutral product II from any acidic product that may be formed in the addition of dinitrogen trioxide to 1-phenylcyclohexene (I). This would explain the erratic yields of V that were encountered in experiments performed[9] subsequent to the original publication,[2] since the ether solution of the products at that stage (see Experimental) would contain varying amounts of oxides of nitrogen depending upon the extent of washing of the ether layer, duration of drying etc. Confirmation of the possible intermediacy of II in the formation of the oxime V was obtained by treatment of II with amyl nitrite in the presence of an equivalent of sodium methoxide, whereby a fair yield of V was obtained.

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured with a Beckmann Model DU Spectrophotometer. Infra-red spectra were measured by Mr. S. Selvavinayakam using a Perkin-Elmer Infracord Spectrophotometer.

3-Nitro-2-phenyl-2-cyclohexenone oxime

(*a*) *From 1-phenylcyclohexene.* A mixture of saturated aqueous solution of sodium nitrite (50 ml) and 1-phenylcyclohexene (2 g) in ether (50 ml) was cooled in ice-water and treated with 4N H_2SO_4 added in drops till the blue colour changed to yellow. After the mixture was left aside for several hours, the ether layer was separated, washed well with water and dried (Na_2SO_4). The combined ether extracts from 5 such experiments were treated with a solution of sodium methoxide (2·5 g) in absolute methanol (35 ml) with vigorous shaking.[2] Water (40 ml) was added to the solution with stirring and the deep red aqueous layer separated. Acidification of the alkaline solution and crystallization of the precipitate from alcohol gave the *oxime* V (0·5–3 g) as yellow needles, m.p. 227–228° (decomp) (Found: C, 62·0, 62·1, 62·2; H, 5·2, 5·2, 5·4; N, 11·8, 11·9; active H, 0·38. $C_{12}H_{12}N_2O_3$ requires: C, 62·1; H, 5·2; N, 12·1; 1 active H, 0·43%). The *acetate* was made in quantitative yield by the action of acetic anhydride in pyridine at 100° for 1 hr and was obtained by crystallization from aqueous methanol as light brown needles, m.p. 103–104° (Found: C, 61·4, 61·1; H, 5·2, 5·2; N, 10·7. $C_{14}H_{14}N_2O_4$ requires: C, 61·3; H, 5·1; N, 10·2%). Hydrolysis of the acetate using 10% methanolic potassium hydroxide at 30° for 1 hr regenerated the oxime in good yield.

(b) *From 2-nitro-1-phenylcyclohexene.* A mixture of 2-nitro-1-phenylcyclohexene[2] (5 g) and amyl nitrite (5 g) in dry methanol (25 ml) was treated with a solution of sodium (1·5 g) in methanol (20 ml). The reaction mixture was left overnight at room temp and then poured into excess water. The solution

[8] H. Cromwell, Q. T. Wiles and O. C. Schroeder, *J. Amer. Chem. Soc.* **64**, 2432 (1942).
[9] V. N. Sundararajan, Ph.D. Thesis, Madras University, August (1957).

was cooled and repeatedly extracted with ether. The aqueous alkaline layer was then cooled well and made acidic with HCl, when a yellow solid (3 g) was precipitated. Crystallization of this material from methanol yielded needles of the oxime (1·1 g), m.p. and mixed m.p. 227° (decomp).

3-Nitro-2-phenyl-2-cyclohexenone

A suspension of the oxime (2 g) in 4 N H_2SO_4, (40 ml) and dioxane (20 ml) was refluxed for 2 hr. The solid dissolved gradually and an oily layer separated. The mixture was poured into ice-water and the precipitate filtered and washed with water. This was dissolved in boiling methanol (100 ml), decolourized with animal charcoal and filtered. The filtrate was concentrated to 20 ml, treated with water to turbidity and cooled. The precipitate was filtered and washed with benzene to leave a little (ca. 0·1 g) of the original oxime, m.p. 220–225°. The benzene filtrate was evaporated to give the *ketone* VI (1 g), m.p. 105–106°, which on a second crystallization from methanol, formed glistening yellow plates, m.p. 109–110° (Found: C, 66·3, 66·4; H, 5·1, 5·0; N, 6·3, 6·4. $C_{12}H_{11}NO_3$ requires: C, 66·4; H, 5·1; N, 6·5%). The ketone (0·1 g) and hydroxylamine hydrochloride (0·1 g) in alcohol (1 ml) and pyridine (1 ml) heated at 100° for 1·5 hr, afforded, after crystallization from alcohol, yellow needles of the oxime (0·1 g), m.p. and mixed m.p. with V, 226–227° (decomp). The *semicarbazone* made by the sodium acetate procedure, on crystallization from aqueous alcohol, formed golden yellow needles, m.p. 207–208° (decomp) (Found: C, 56·7; H, 4·7. $C_{13}H_{14}N_4O_3$ requires: C, 56·9; H, 5·1%). The *2,4-dinitrophenylhydrazone* was obtained as orange plates (from benzene–alcohol), m.p. 202–203°, λ_{max} 380 mμ (log ε 4·45) (Found: C, 54·1, H, 3·5. $C_{18}H_{15}N_5O_6$ requires: C, 54·4; H, 3·8%).

Sodium borohydride reduction of ketone VI

A solution of the ketone (0·2 g) in methanol (10 ml) was reduced with sodium borohydride (0·2 g) to give the crude product (0·15 g) as a gum. Fractional crystallization of the petroleum ether (b.p. 40–60°) soluble fraction of the product gave crystals (20 mg) which were recrystallized from the same solvent to give the *nitroalcohol*, m.p. 110°, with softening above 103°, depressed by admixture with the ketone VI (Found: C, 65·1; H, 6·7. $C_{12}H_{15}NO_3$ requires: C, 65·2; H, 6·8%).

Lithium aluminium hydride reduction of the ketone VI

A solution of the ketone (2 g) in tetrahydrofuran (10 ml) and ether (50 ml) was added during the course of 1 hr, to lithium aluminium hydride (3 g) in ether (50 ml). The mixture was stirred for 8 hr, left overnight and decomposed with water. The ether layer was decanted and the sludge extracted repeatedly with chloroform (3 × 150 ml). The combined extracts were evaporated and the residue taken up in ether (100 ml) and extracted with 2 N H_2SO_4 (50 ml). The aqueous layer was separated and the oily base (1·35 g) obtained from it by basification was converted into the hydrochloride. Fractional crystallization from alcohol–ether afforded as the less soluble fraction, a crop of crystals (70 mg), which on recrystallization yielded the hydrochloride of one isomer of *3-amino-2-phenylcyclohexanol*, m.p. 327–330° (decomp) (Found: C, 63·8; H, 7·9; N, 6·0. $C_{12}H_{18}ClNO$ requires: C, 63·3; H, 7·9; N, 6·1%). The more soluble fraction was obtained from the mother liquors as stout crystals (0·8 g), m.p. 237–239°. Recrystallization from alcohol–ether gave an isomeric *hydrochloride*, m.p. 241° (Found: C, 63·3; H, 8·0, N, 5·9%).

Ethylene ketal of 3-nitro-2-phenyl-2-cyclohexenone

A mixture of the ketone VI (1 g) and *p*-toluenesulphonic acid (50 mg) in benzene (50 ml) containing ethylene glycol (4 ml) was refluxed for 2–3 hr. The solvents were then removed *in vacuo* and the residue taken up in ether. The ether layer was washed with sodium bicarbonate solution and then with water. The product obtained from the dried ether layer was crystallized from ether–pet ether (b.p. 40–60°) to afford the *ketal* (0·8 g), m.p. 84° (Found: C, 64·1; H, 5·6. $C_{14}H_{15}NO_4$ requires: C, 64·4; H, 5·8%).

Ethylene ketal (VIII) *of 3-amino-2-phenylcyclohexanone*

A solution of the ketal (0·5 g) in ether was added during the course of ½ hr to lithium aluminium hydride (1 g) in ether (50 ml). After being left overnight, the mixture was decomposed with water and the basic product, obtained from the ether layer, was purified by one passage through dil HCl. The

semisolid base (0·35 g) was converted into the hydrochloride. Fractional crystallization from alcohol–ether gave a less soluble crop of crystals which was recrystallized to give a hydrochloride of VIII,[7] m.p. 232° (decomp). From the mother liquors by dilution with more ether, an isomeric *hydrochloride* was obtained, m.p. 214–216° (decomp) (Found: C, 62·3; H, 7·1. $C_{14}H_{20}ClNO_2$ requires: C, 62·3; H, 7·4%).

Hydrolysis of the aminoketal VIII

A solution of the crude aminoketal (1 g) in 4N HCl (15 ml) was heated on the steam bath for 2 hr. The solution was diluted and extracted with ether. The ether extract was washed successively with water, aqueous sodium bicarbonate and again water. Removal of solvent from the ether layer and crystallization of the residue from ether gave colourless crystals of 2-phenyl-2-cyclohexenone (IX), m.p. 98° (Found: C, 83·3; H, 6·7. $C_{12}H_{12}O$ requires: C, 83·7; H, 7·0%), identical with an authentic specimen synthesized[10] by hydrolysis of its oxime obtained by the addition of nitrosyl chloride to 1-phenylcyclohexene. Identity was further confirmed by comparison of the oxime, m.p. 151° and 2,4-dinitrophenylhydrazone, m.p. 165–166° of the ketone with authentic samples.[10]

3-*Nitro*-2(o-*tolyl*)-2-*cyclohexenone oxime*

Treatment[2] of 1-(*o*-tolyl)cyclohexene (10 g) with dinitrogen trioxide gave as the alkali soluble fraction, the *oxime* (2 g) which formed yellow needles (from alcohol), m.p. 210° (decomp) (Found: C, 63·1; H, 5·9. $C_{13}H_{14}N_2O_3$ requires: C, 63·4; H, 5·7%) further characterized as its *acetate*, pale yellow needles (from aqueous methanol), m.p. 99° (Found: C, 62·7; H, 5·7. $C_{15}H_{16}N_2O_4$ requires: C, 62·5; H, 5·6%).

Hydrolysis of the oxime (1 g) with 4N H_2SO_4 (20 ml) in dioxane (10 ml) for 2 hr gave 3-*nitro*-2-(o-*tolyl*)-2-*cyclohexenone* as pale yellow prisms, m.p. 119–121° (Found: C, 67·9; H, 5·4. $C_{13}H_{13}NO_3$ requires: C, 67·5; H, 5·6%), yielding a 2,4-*dinitrophenylhydrazone*, orange needles (from benzene–alcohol), m.p. 217° with slight softening above 209°, λ_{max} 380 mμ (log ε 4·48) (Found: C, 55·4; H, 4·2. $C_{19}H_{17}N_5O_6$ requires: C, 55·5; H, 4·1%).

3-*Nitro*-2-(m-*tolyl*)-2-*cyclohexenone oxime*

1-(*m*-Tolyl)cyclohexene (10 g) by treatment with dinitrogen trioxide[2] gave the *oxime* (2 g) which crystallized from alcohol in pale yellow needles, m.p. 195–197° (Found: C, 63·1; H, 5·4%), forming an *acetate*, m.p. 117° (Found: C, 62·6; H, 5·8%).

Acid hydrolysis of the oxime (1 g) as before gave 3-*nitro*-2-(m-*tolyl*)-2-*cyclohexenone* (0·5 g) as an oil which solidified after being left overnight in the ice-chest. Recrystallized from aqueous methanol, it formed pale yellow needles, m.p. 82–83° (Found: C, 67·4; H, 5·3%). The 2,4-*dinitrophenylhydrazone* was obtained as brownish red needles (from benzene–alcohol), m.p. 204–206° (decomp), λ_{max} 383 mμ (log ε 4·40) (Found: C, 55·3; H, 4·1%).

3-*Nitro*-2-(p-*tolyl*)-2-*cyclohexenone oxime*

Reaction of 1-(*p*-tolyl)cyclohexene (10 g) with dinitrogen trioxide gave the *oxime* (1·5 g) which was recrystallized from alcohol in yellow needles, m.p. 228° (decomp) (Found: C, 63·4; H, 5·7%), forming an *acetate*, colourless needles (from aqueous methanol), m.p. 79–81° (Found: C, 62·9; H, 5·7%).

Sulphuric acid hydrolysis of the oxime (1 g) yielded 3-*nitro*-2-(p-*tolyl*)-2-*cyclohexenone* (0·55 g), yellow needles, m.p. 98–100° (Found: C, 67·3; H, 5·4%), giving a 2,4-*dinitrophenylhydrazone*, orange needles, m.p. 215–216°, λ_{max} 383 mμ (log ε 4·60) (Found: C, 55·9; H, 4·1%).

3-*Nitro*-2-(m-*anisyl*)-2-*cyclohexenone oxime*

1-(*m*-Anisyl)cyclohexene (10 g) by treatment with dinitrogen trioxide[2] yielded as the alkali soluble product, the *oxime* (1·5 g), pale brown needles (from alcohol), m.p. 161° (Found: C, 59·4; H, 5·7. $C_{13}H_{14}N_2O_4$ requires: C, 59·5; H, 5·4%), further characterized as the *acetate*, colourless needles (from methanol) m.p. 137° (Found: C, 59·2; H, 5·6. $C_{15}H_{16}N_2O_5$ requires: C, 59·2; H, 5·3%).

[10] David Ginsburg and Raphael Pappo, *J. Chem. Soc.* 516 (1951).

The above oxime (0·8 g), hydrolysed by hot sulphuric acid afforded *3-nitro-2-(m-anisyl)-2-cyclohexenone* (0·4 g) as an oil which solidified after being left in the ice-chest. Recrystallized from benzene–pet ether (b.p. 40–60°) it formed yellow needles m.p. 67–69° (Found: C, 63·3; H, 4·9. $C_{13}H_{13}NO_4$ requires: C, 63·2; H, 5·3%). The *2,4-dinitrophenylhydrazone* crystallized from benzene–alcohol as orange-red plates, m.p. 163–164°, λ_{max} 380 mμ (log ε 4·54) (Found: C, 53·7; H, 3·6. $C_{19}H_{17}N_5O_7$ requires: C, 53·4; H, 4·0%).

Nitroacetone 2,4-dinitrophenlyhydrazone

The *hydrazone* was made from nitroacetone[11] and was recrystallized from alcohol in glistening yellow plates, m.p. 137–139° (Found: C, 38·2; H, 2·9. $C_9H_9N_5O_6$ requires: C, 38·2; H, 3·2%).

Acknowledgement—We are grateful to Mr. S. Selvavinayakam for the microanalyses. We thank the Government of Madras for the award of a Research Assistantship (to V. N. S.).

[11] C. Harries, *Liebig Ann*, **319**, 251 (1901).

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THE STRUCTURE OF MELANINS AND MELANOGENESIS—I

THE STRUCTURE OF MELANIN IN *SEPIA*[1]

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Abstract—Melanin from *Sepia officinalis* is a natural polymer containing many carboxylic groups. It is present in the ink sac of the animal as the Mg and Ca salt. Purified sepiomelanin is able to combine with cations and, to a less extent with anions; by heating CO_2 is evolved. A formula closely related to . . . [—$C_5H_3O_2N$—$C_5H_4O_2N$·COOH—]$_x$. . . is suggested for sepiomelanin and its derivatives.

Owing to the presence of a tyrosinase in the ink sack it is possible that 2-carboxy-2,3-dihydroindole-5,6-quinone (dopachrome) plays an important part in the biological process of polymerization.

THE chemistry of melanins is still obscure in spite of the work accomplished.[2] For example, the composition of a natural melanin is yet unknown and consequently, the relations between the various natural, biosynthetic and synthetic pigments are unknown.[3] Chemically, the natural melanin of *Sepia* has been most studied.[4] This pigment is found in the so-called "ink sac" of *Sepia* (Fig. 1). One or two grams of melanin can be obtained from an average-sized animal—a large amount in relation to the body weight (300–400 g). The ink is easily collected by cutting open and lightly squeezing the ink sac. The melanin in the ink occurs in the form of small granules suspended in a colourless plasma.

The biological function of melanin appears to be defensive but the mechanism is uncertain.[5]

It is known that the ink gland contains an enzyme capable of converting tyrosine into melanin,[6] and it may be assumed that the mechanism described by Raper *et al.*[7]

[1] This investigation was supported by the National Cancer Institute, Research Grant C. 5220, Public Health Service, U.S.A.

[2] The literature of melanin chemistry is excellently reviewed by: A. Quilico, *I pigmenti neri animali e vegetali* Tip. Fusi, Pavia (1937); H. S. Mason in M. Gordon, *Pigment Cell Growth* AP. New York; H. S. Mason in F. F. Nord, *Advances in Enzymology* Vol. XVI. IP. New York (1955); H. S. Masonin M. Gordon, *Pigment Cell Biology* AP. New York (1959).

[3] Notably tyrosine melanin, catecol melanin and pyrrole black.

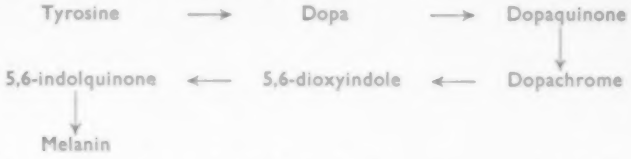
[4] L. Panizzi and R. A. Nicolaus, *Gazz. Chim. Ital.* **82,** 435 (1952); R. A. Nicolaus, *Ibid.* **83,** 239 (1953); **85,** 659 (1955); R. A. Nicolaus and L. Mangoni, *Ibid.* **85,** 1397 (1955); R. A. Nicolaus and L. Caglioti, *Ric. Sci.* **27,** 113 (1957); R. A. Nicolaus, A. Vitale and M. Piattelli, *Rend. Acc. Sci. Fis. Mat. Napoli* Vol. XXV (1958); R. Scarpati and R. A. Nicolaus, *Ibid.* Vol. XXVI (1959); R. A. Nicolaus, M. Piattelli and G. Narni, *Tetrahedron Letters* No. 21 (1959); R. A. Nicolaus, M. Piattelli and G. Narni, *Rend. Acc. Sci. Fis. Mat. Napoli* Vol. XXVII (1960).

[5] D. Tompsett, *Memoirs on Typical British Marine Plants and Animals* Vol. XXXII. University Press, Liverpool (1939).

[6] H. Pribram, *Hofm. Beitr.* **1,** 229 (1901); C. Gessard, *Compt. Rend. Soc. Biol.* **54,** 1304 (1902); P. Rondoni, *Sperimentale* **75,** 33 (1921); L. Califano, *Pubbl. Staz. Zool. Napoli* **13,** 289 (1933); L. Califano and D. Kertész, *Enzymology* **6,** 233 (1939).

[7] H. S. Raper, *Biochem. J.* **21,** 89 (1927); W. L. Dulière and H. S. Raper, *Ibid.* **24,** 239 (1930); R. D. H. Heard and H. S. Raper, *Ibid.* **27,** 36 (1933); see also H. S. Mason, *J. Biol. Chem.* **172,** 83 (1948).

may be applied to the formation of the pigment *in vivo*. It should, therefore, be considered as a polymer of 5,6-indolquinone:



The problem of purifying melanin from *Sepia* was never seriously faced, and only

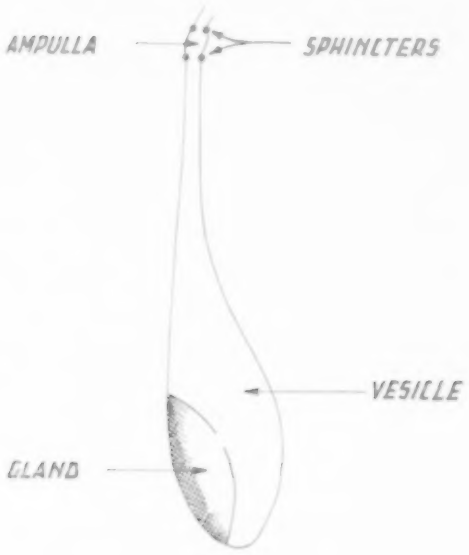


FIG. 1.

recently have two simple methods been put forward which give encouraging results. The first consists, briefly, of the following processes:

(a) washing the pigment with 1 per cent HCl.
(b) hot extraction with acetone.
(c) prolonged boiling with concentrated HCl.

The second method involves:

(a) dialysis of the contents of the ink sac against distilled water.
(b) washing with 1 per cent HCl.
(c) digestion for 370 hours with concentrated HCl.[8]

During purification it was observed that melanin is combined with calcium and magnesium. Melanin may also combine with small quantities of acid (in this case HCl) and may lose CO_2 on heating.[9]

The amorphous pigment obtained was hygroscopic, insoluble in all solvents, did not crystallize and contained traces of sulphur (0·2–0·4 per cent). The substance

[8] These methods of purification remove proteins and inorganic material. The nature of this material will be reported soon. It is notable that on oxidation it yields no pyrrolic acids.
[9] These properties explain the disagreement of analytical data in the literature.

obtained according to the first method of purification was entirely free from ashes and on analysis corresponded with a polymer of Type I or better, Type II.[10]:

$$\ldots\ldots[-(C_9H_9O_2N)_4-C_9H_7O_2N{\cdot}COOH-]_x\ldots\ldots \quad \text{I}$$

$$\ldots\ldots[-(C_9H_9O_2N)_4-C_9H_6O_2N{\cdot}COOH-]_x\ldots\ldots \quad \text{II}$$

$$\ldots\ldots[-C_9H_9O_2N-C_9H_7O_2N{\cdot}COOH-]_x\ldots\ldots \quad \text{III}$$

$$\ldots\ldots[-C_9H_9O_2N-C_9H_6O_2N{\cdot}COOH-]_x\ldots\ldots \quad \text{IV}$$

The second method of purification performed at room temperature, gave a less pure substance but the danger of decarboxylation was avoided. Analysis of this pigment agreed with that of a polymer of Type III, or better Type IV.

The presence of carboxyl groups in sepiomelanin has been proved by the following observations:

(a) the carboxyl groups could be titrated with alkali.

(b) CO_2 was evolved on heating at 140°–150°.

(c) a methyl ester was obtained on treatment with methyl alcohol in the presence of hydrogen chloride.

Moreover, quantitatively, the number of the —COOH groups deducible from the analytical results shown in Table I agree satisfactorily with the formulae given, provided that the special physical properties of the substance are taken into account and because of these properties it is not possible to expect reactions to proceed to completion.

TABLE I

	Found	Calculated
Neutralization equivalent of melanin:	306	338·3
Percentage CO_2 evolved at 140°–150°:	9·1	13·0
Percentage OCH_3 of the methyl ester:	6·0	8·8

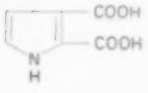
The behaviour of the pigment with diazomethane is interesting. A compound was obtained which on analysis gave values near the theoretical for a polymer .... $[-C_9H_7O_2N-C_9H_6O_2N{\cdot}COOCH_3-]_x$ ..... This indicates the presence of numerous hydroxyl groups or desmotropic functions. The percentage value of methoxyl found (18·8) was much lower than that calculated for polymer IV (24·4). Probably, by reason of its complete insolubility, the pigment is never entirely methylated (on heating small quantities of carbon dioxide are still evolved) and some units of the polymer can also react as orthoquinones with diazomethane. This can be demonstrated qualitatively by the positive colour test for —O—CH_2—O— group.[11] We have also been able to show that diazomethane reacts slightly with nitrogen; in fact,

[10] These formulae and other like them show only the statistical distribution of the two types of units in the polymer.

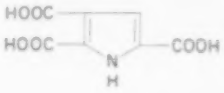
[11] Indirectly this is the only proof of the existence of orthoquinone groups in the melanin of *Sepia*.

on oxidation of the methylated pigment with $KMnO_4$, monomethylamine is obtained. This is not formed from melanin under similar conditions.

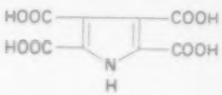
The most important compounds isolated or identified from the products of oxidation with H_2O_2 or $KMnO_4$ are, as is known, pyrrolic acids V, VI and VII:



V



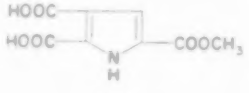
VI



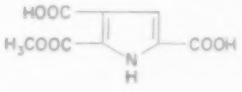
VII

Pyrrolic acids V and VI have been isolated, but pyrrolic acid VII has only been identified by paper chromatography. The yields of these acids are low: 1–2 per cent for pyrrolic acid VI and less than 0·05 per cent for the other two. However, as we shall see, these acids have a certain significance for structural investigation.

The behaviour of methylated melanin on oxidation is different because the pyrrolic acids V, VI and VII disappear almost completely from the degradation products. This is easily shown by chromatography. When chromatograms are sprayed with DZA the pyrrolic acids are recognizable as intense red spots. In the case of methylated melanin, however, a yellow spot is visible, with an R_f near that of pyrrolic acid VI. But if the degradation products are hydrolysed with NaOH and chromatographed, this yellow spot disappears and a spot identifiable with pyrrolic acid VI appears instead. Considering the R_f value of the yellow spot and the colour which is characteristic of esterified pyrrolic acids in the α-position, one must presume that such a spot is caused by an ester of Type VIII or IX:



VIII

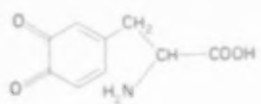


IX

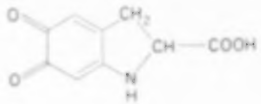
Since it is very probable that the carboxyl groups in position 4 and 5 are derived from the destroyed benzenoid portion of the pigment, one has to conclude that the ester in question is 2-carbomethoxy-4,5-dicarboxypyrrole (VIII). This indicates that pyrrolic acid VI is derivated essentially from the carboxylated units of the pigment. This was confirmed by comparing chromatographically the oxidation products of sepiomelanin before and after heating at 140°–150°. Melanin purified at low temperature yielded traces of 2,3-pyrroledicarboxylic acid V and 2,3,4,5-pyrroletetracarboxylic acid VII, and large quantities of 2,3,5-pyrroletricarboxylic acid VI. With melanin heated at 140°–150° the amount of pyrrolic acid VI clearly decreased, whereas pyrrolic acid V was found in relatively large quantities. This also makes it clear that pyrrolic acid VI derives from carboxylated units of the pigment and pyrrolic acid V from decarboxylated units.

These results are easily interpreted if one partially accepts Raper's mechanism of melanin formation. However, the higher hydrogen content than that calculated for a polymer of formula $(C_8H_5O_2N)_x$ and the presence of a large number of carboxylic groups in sepiomelanin lead one to think that polymerization occurs with the participation of a compound carrying a —COOH group. The possible monomers are

dopaquinone (X) and dopachrome (XI):



X



XI

With X a polymer should contain α-aminoacid chains.[12] In order to show the possible presence of groups of this type, sepiomelanin was methylated with diazomethane and oxidized with $KMnO_4$. The volatile basic products were analysed by gas chromatography (see Figs. 2 and 3).

It has only been possible to show the presence of ammonia and methylamine. If

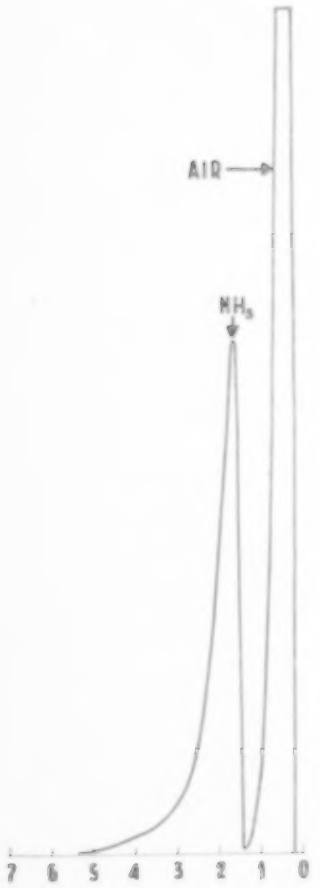


FIG. 2.

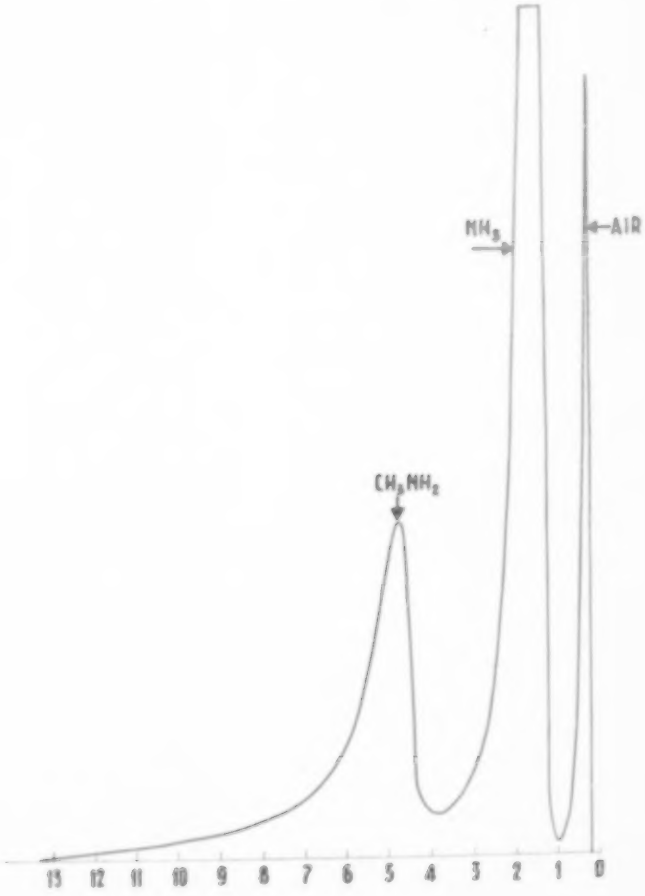


FIG. 3.

[12] This was considered unlikely since 6-methyldopa, which cannot be transformed into indolequinone, does not form melanin (R. I. T. Cromartie and J. Harley-Mason, *Biochem. J.* **66**, 713 (1957). The degradation described here was performed as a further control.

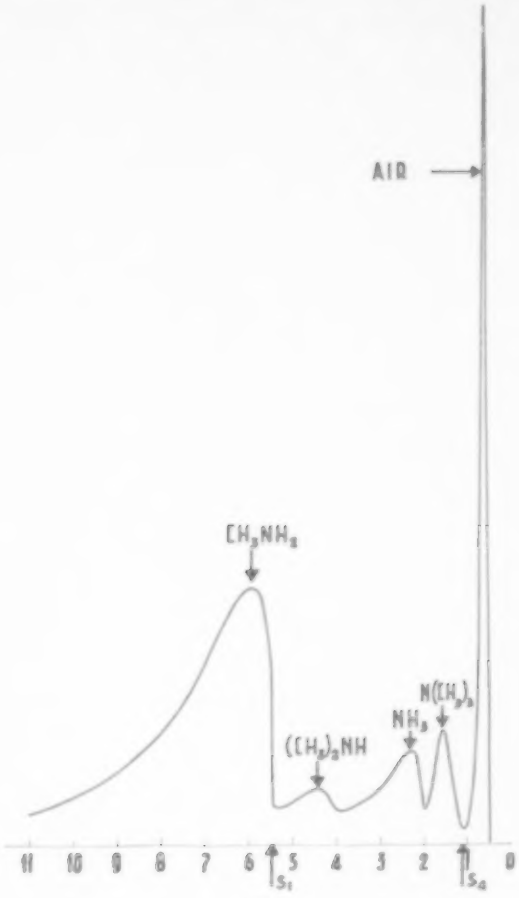
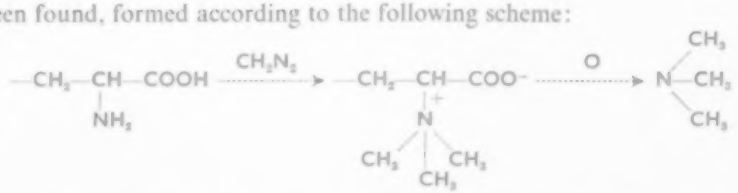


FIG. 4.

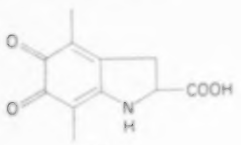
chains of the type $-CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$ had been present, trimethylamine would have been found, formed according to the following scheme:

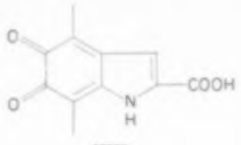


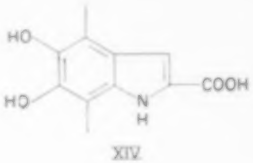
As a control, a sample of tyrosine was methylated with diazomethane and oxidized with $KMnO_4$: the presence of trimethylamine among the volatile degradation products is clear from the graph (Fig. 4).

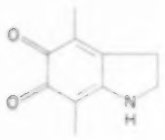
The presence of dopaquinone units in the polymer being, therefore excluded, one must conclude that dopachrome plays an important part in the biological formation of sepiomelanin.

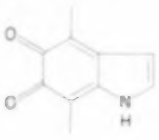
All the results so far obtained can be explained by the presence of units of the following types:

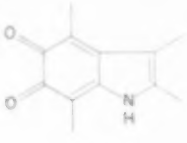

XII

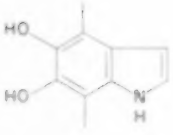

XIII

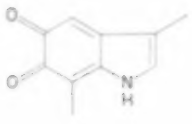

XIV

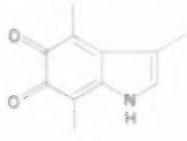

XV


XVI


XVII


XVIII


XIX


XX

Units such as XII, XIII, XIV, may account for the presence of 2,3,5-pyrroletricarboxylic acid VI and 2-carbomethoxy-4,5-dicarboxypyrrole (VIII) among the oxidation products of sepiomelanin and sepiomelanin methyl ether respectively. 2,3-Pyrroledicarboxylic acid V may arise from units of the Type XV, XVI and XVIII.

The possible existence of cross-linking between different chains is depicted in XVII. This structure is supported by the presence of the 2,3,4,5-pyrroletetracarboxylic acid VII in the oxidation mixture.[13]

Finally units XIX and XX, although there is no proof, may not be excluded *a priori* in sepiomelanin, considering the high reactivity of the position 3 in 5,6-dioxyindole derivatives.[14] Although these results seem significant, we think further work is necessary and expect further indications on the structure of sepiomelanin from work now in progress.

EXPERIMENTAL

Hot purification of sepiomelanin

The samples of melanin used were obtained by a method described in a previous paper. The pigment was in the form of a black powder which was infusible, hygroscopic, insoluble in all solvents and contained small quantities of chlorine and traces of sulphur. It was dried in a vacuum over P_2O_5 at 110° for 17 hr. (Found: C, 63·3; H, 2·4; O, 23·8; N, 8·8; Cl, 2·2; S, 0·3–0·4. Subtracting Cl: C, 64·7; H, 2·5; 0, 24·3; N, 9·0. $[-(C_9H_5O_2N)_4-C_9H_5O_2N{\cdot}COOH-]_x$ requires: C, 63·9; H, 2·1; 0, 25·0; N, 9·1%. $[-(C_9H_5O_2N)_4-C_9H_4O_2N{\cdot}COOH-]_x$ requires: C, 63·2; H, 3·2; O, 24·7; N, 9·0%). No ashes were left on calcination. Melanin samples are very difficult to burn. Differences of 1–2% were observed in various analyses of the same sample.

[13] According to M. M. Rangier, *C. R. Acad. Sci., Paris* **249**, 1954 (1959) the fundamental unit of natural melanins is adrenochrome. Unfortunately, the paper is so erroneus that it cannot be considered.

[14] J. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 703, 2248 (1951); R. I. T. Cromartie and J. Harley-Mason, *Ibid.* 3525 (1953); *Idem., Biochem. J.* **66**, 713 (1957).

Cold purification of sepiomelanin

An ink sac was taken from an urethan-anesthetized cuttlefish, cut open and emptied. The liquid obtained, which was slightly alkaline, was dialysed against distilled water until the reaction for Cl^- was negative. The dialysed fluid, after evaporation in a vacuum, left 71 mg of residue.

The content of the dialysis tube, plus 50 cc 1% HCl, was centrifuged. The black precipitate was washed by centrifuging 5 times with 1% HCl (20 cc each time).

The combined supernatants gave 10·2 mg residue after evaporation and calcination. Analysis of the residue by flame spectrophotometry showed it to consist of magnesium and calcium chlorides in a molecular ratio of 1:1·76.

The pigment was then suspended in 15 cc conc HCl and left at room temp for 15 days. It was then centrifuged, washed 10 times with 1% HCl (20 cc each time) and twice with distilled water; 24 mg of residue were obtained from the washings.

After drying over P_2O_5 in a vacuum at room temp for 48 hr, the purified pigment weighed 140 mg. Analysis showed a chlorine content of about 3%, only partially removable by dialysis, traces of sulphur and negligible quantities of ashes, but the pigment was considered sufficiently pure for investigation. Boiling for 24 hr with conc HCl removed small quantities (2–4%) of colourless material mostly consisting of aminoacid hydrochlorides and traces of inorganic substances. (Found: C, 59·9; H, 3·4; O, 26·3; N, 8·2; Cl, 3·2; S, 0·3–0·4. Subtracting Cl: C, 60·9; H, 3·4; O, 27·1; N, 8·5. $[—C_9H_5O_2N—C_9H_2O_2N{\cdot}COOH—]_x$ requires: C, 61·1; H, 1·8; O, 28·7; N, 8·4% $[—C_9H_5O_2N—C_9H_4O_2N{\cdot}COOH—]_x$ requires: C, 60·9; H, 3·0; O, 28·4; N, 8·3%). No ashes were left on calcination. Drying the samples of melanin in a vacuum at higher temp (80° and 110°) does not alter the pigment.

Methyl ester

100 mg of finely ground melanin were suspended at room temp in 2·5 cc anhydrous methanol, saturated with dry hydrogen chloride. After 24 hr the solid was centrifuged, washed with anhydrous methanol, dried in air, triturated again and re-esterified.

After repeating 3 times, the reaction was considered complete since the amount of methoxyl found did not increase. The samples of esterified melanin were dried to a constant weight in a vacuum at room temp. The ester was in the form of a black powder, insoluble in all solvents and containing traces of sulphur and small quantities of chlorine. (Found: C, 58·9; H, 3·3; O, 26·0; N, 7·9; Cl, 3·9; S 0·3; OCH_3, 5·7. Subtracting Cl: C, 61·2; H, 3·5; O, 27·1; N, 8·0; OCH_3, 6·0. $[—C_9H_5O_2N—C_9H_2O_2N{\cdot}COOCH_3—]_x$ requires: C, 62·1; H, 2·3; O, 27·6; N, 8·0; OCH_3, 8·9%. $[—C_9H_5O_2N—C_9H_4O_2N{\cdot}COOCH_3—]_x$ requires: C, 61·4; H, 3·4; O, 27·3; N, 7·9; OCH_3, 8·8%). On oxidation with permanganate the ester behaves in a very similar way to sepiomelanin. Pyrrolic acids V, VI and VII were always obtained, although the tricarboxylic acid VI diminished. On heating under the conditions described later CO_2 was evolved to the extent of 2·8% of the weight of pigment used.

Methyl ether

100 mg of finely ground melanin was treated with an ethereal solution of diazomethane (200 mg diazomethane in 2 cc ether) and allowed to stand at room temp. After 24 hr the melanin was centrifuged, washed with ether, ground up again and treated with diazomethane. The process was repeated 3 times. After washing with ether and anhydrous methanol the pigment was dried for 48 hr at room temp over P_2O_5 in a vacuum. The methyl ether was in the form of an infusible brown powder, insoluble in all solvents. On heating to 140°–150°, CO_2 was evolved to the extent of 1·8% by weight of the pigment. The —O—CH_2—O— group test was positive and performed as follows: 50 mg of methylated pigment were suspended in 5 cc conc H_2SO_4 and treated with 0·2 cc of 0·5% alcoholic solution of gallic acid. After leaving overnight and then centrifuging the pigment, the liquid was coloured emerald green. (Found: C, 64·1; H, 5·5; O, 23·8; N, 7·4; OCH_3, 18·8. $[—C_9H_5O_2N—C_9H_4O_2N{\cdot}COOCH_3—]_x$ requires: C, 63·8; H, 3·2; O, 25·5; N, 7·5; OCH_3, 24·7%. $[—C_9H_7O_2N—C_9H_6O_2N{\cdot}COOCH_3—]_x$ requires: C, 63·1; H, 4·2; O, 25·3; N, 7·4; OCH_3, 24·4%).

Determination of carboxyl groups by titration

570 mg of melanin were placed in a glass column of diameter 8 mm, a N/5 solution of Na_2CO_3 was passed through the column and the first 100 cc were collected. By titration with N/5 HCl

(indicator tetrabromophenolphthalein ethyl ester or fluorescein in u.v. light) a neutralization equivalent of 306 was determined (theoretical neutralization equivalent for $[—C_5H_5O_2N—C_5H_4O_2N·COOH]_x = 338·3$). In the calculation the amount of alkali used to neutralize the hydrochloric acid in the pigment was allowed for.

Thermic decarboxylation of sepiomelanin

Melanin, obtained as described above, was finely ground, suspended in 5 cc vaseline oil and heated at 140°–150° (bath temp) for 10 hr in a current of nitrogen. The amount of CO_2 evolved was measured by absorbing the gas in a saturated solution of barium hydroxide and weighing the barium carbonate formed; 0·4292 g $BaCO_3$ was obtained from 1·0817 g melanin, and was equivalent to 0·0957 g CO_2 (8·85% of the weight of melanin used). Subtracting the chlorine present in the sample, a value of 9·1% is obtained. The theoretical carbon dioxide evolved by a polymer $[—C_5H_5O_2N—C_5H_4O_2N·COOH—]_x$ is 13·0%.

The decarboxylated melanin was washed repeatedly with light petroleum (b.p. 40°–70°) and finally with ether; it was then dried for 48 hr over P_2O_5 in a vacuum. (Found: C, 61·1; H, 3·5; O, 22·0; N, 9·2; Cl, 4·0. Subtracting Cl: C, 63·5; H, 3·6; O, 22·9; N, 9·5. $(C_5H_5O_2N)_x$ requires: C, 65·3; H, 3·4; O, 21·7; N, 9·5%). Decarboxylated melanin was in the form of a black powder, infusible, hygroscopic and insoluble in all solvents. No apparent difference could be observed between it and the original melanin.

Determination of the water content of melanin

After desiccation melanin was highly hygroscopic; the rate of water absorption was very rapid at first, but gradually decreased, although it was still noticeable after many days. In an atmosphere saturated with water vapour at 20° the quantity of water absorbed after 15 days was 30% of the original weight of melanin.

By drying over P_2O_5 in a vacuum the water was totally removed and the original weight of melanin was restored. Drying at various temperatures (room temp; 80°; 110°) varied only the time required for water removal.

Comparative oxidation of sepiomelanin and decarboxylated sepiomelanin

Quantitative chromatographic analysis of pyrrolic acids. 100 mg of melanin and 100 mg of decarboxylated melanin were each suspended in 2 cc 2N K_2CO_3 and oxidized with 3% $KMnO_4$ until the colour persisted for 15 min.

For oxidation, melanin required 12·5 cc. $KMnO_4$ and decarboxylated melanin required 12·7cc. After removal of MnO_2 and precipitation of oxalic acid with $CaCl_2$ the solutions were extracted with ether (50 cc in 5 portions). After removal of the solvent, melanin yielded 7·6 mg residue and decarboxylated melanin 3·5 mg. These residues were each dissolved in distilled water and the filtered solutions used for quantitative determination of 2,3,5-pyrroletricarboxylic acid VI and 2,3-pyrroledicarboxylic acid V. For this analysis 0·1 cc of each solution and graduated quantities (0·025 cc, 0·10 cc, 0·15 cc) of a standard solution containing 1 mg 2,3,5-pyrroletricarboxylic acid VI per cc were applied to a Whatman No. 1 paper. Descending chromatography, using ethanol–33% ammonia–water (80:4:16) as solvent, was allowed to run to about 25 cm from the starting point. After colour development with DZA the spots were cut out and their colours eluted in 20 cc N/20 Na_2CO_3 solution. The optical densities of these solutions were read with a Lumetron colorimeter (filter $\lambda = 420$ mμ) using a blank made from part of the paper sprayed with DZA. From the calibration curve the quantity of 2,3,5-pyrroletricarboxylic acid VI contained in the samples was easily determined.

The 2,3,5-pyrroletricarboxylic acid content of melanin was found to be 1·4%, and that of decarboxylated melanin 0·5%.

The 2,3-pyrroledicarboxylic acid V content was determined by the same method. Decarboxylated melanin gave approximately 0·05% of this acid. Carboxylated melanin, however, gave quantities that they were not measurable by this method.

Oxidation by $KMnO_4$ of the fractions soluble in water and hydrochloric acid

(a) The residues obtained by evaporation of the dialysate and of the washing of raw melanin with 1% HCl resisted oxidation by permanganate under the conditions described and used for melanin

(b) On permanganate oxidation the fraction removable with cold conc HCl yielded small quantities of substances that can be revealed with DZA. Such spots have R_f values differing from those of 2,3-pyrroledicarboxylic acid V, 2,3,5-pyrroletricarboxylic acid VI and 2,3,4,5-pyrroletetracarboxylic acid VII.

Volatile bases from oxidation of melanin and its methyl ether

Examination by gas chromatography. Melanin and its methyl ether were oxidized with $KMnO_4$ as described above. At the end of oxidation the liquid was distilled and collected in N HCl. The hydrochlorides of the volatile bases were obtained by evaporation of the acidic solutions. The yield from melanin was about 10% of the oxidized weight of the pigment and from methylated melanin 13%.

The hydrochlorides were treated with the minimum possible quantity of a saturated solution of KOH and the bases analysed by gas chromatography using C. Erba's Fractovap apparatus. The composition of the column (1 m length) was: celite 85%, triethanolamine 7·5%, vaseline oil 7·5%. The carrier gas was hydrogen, at a flow rate of 4 litres per hour. The experiment was carried out at 20°. Results are shown in (Figs. 2 and 3), melanin yielded only ammonia (Fig. 1), while methylated melanin yielded ammonia and methylamine (Fig. III).

By indirect analysis of the hydrochlorides (Mohr's or Volhard's determination of Cl^-) ammonium chloride and methylamine hydrochloride were found to be in a 1:1 ratio by weight.

Methylation and oxidation with $KMnO_4$ of tyrosine

Examination of the volatile bases. 100 cc of an ethereal solution containing 2·5 g diazomethane were added to 100 cc of an ethereal suspension of 1 g tyrosine. Reaction was started with some drops of water. After leaving overnight the ether was evaporated to dryness; the residue was dissolved in 13 cc 2N K_2CO_3 and oxidized with a 3% solution of $KMnO_4$ (135 cc). MnO_2 was filtered off and the liquid distilled and collected in N HCl. The solution was evaporated to dryness and hydrochlorides were examined by chromatography as already described. The results are shown in (Fig. 4).

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CURAMYCIN—I

ISOLATION AND CHARACTERIZATION OF SOME HYDROLYSIS PRODUCTS

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Abstract—From cultures of *Streptomyces cura-coi*, a chlorine containing glycosidic antibiotic, named curamycin, has been isolated. Curamycin on acid hydrolysis yields a crystalline product, curacin, and a mixture of monosaccharides. Curacin, which contains all of the chlorine of curamycin, is the ester of dichloroisoeverninic acid (3,5-dichloro-4-hydroxy-6-methoxy-2-methyl-benzoic acid) with a di-desoxyaldose $C_6H_{12}O_4$, whose structure has not as yet been established. Three other monosaccharides are present, two of which could be identified as L-lyxose and 4-O-methyl-D-fucose.

FROM the culture broth of a new Streptomyces species, *S. curacoi*, isolated from a soil sample collected in the Province of La Pampa, Argentina, a chlorine containing antibiotic, named by us curamycin, has been isolated in crystalline form. Analysis revealed the composition $C_{53-55}H_{82-86}Cl_2O_{32-33}$. It gave a strong positive Molisch test for carbohydrates, the Fehling reaction being negative.

Curamycin inhibits the growth of *S. aureus* in a concentration of 0·125 mg/ml and was found to be stable at pH 7, much less so at pH 9·5 and very unstable at pH 2·0.

Curamycin, which is insoluble in sodium carbonate solution, contains one phenolic group that is responsible for its ready solubility in 0·1 N sodium hydroxide. It does not give a color reaction with ferric chloride, but gives a positive test with Millon's reagent. With diazomethane, a monomethyl curamycin is formed which is insoluble in strong alkalies and gives a negative test with Millon's reagent. The activity against *S. aureus* has also been lost.

When curamycin is heated at 100° with 0·1 N hydrochloric acid for 30 min, a product, representing 26 per cent in weight of the antibiotic, precipitates in crystalline condition, while a partially hydrolyzed mixture of carbohydrates remains in solution.

The crystalline product, which has been named curacin, contains all the chlorine and the phenolic group of curamycin and has the composition $C_{15}H_{16}Cl_2O_7$. Curacin has a pK°_{MCS} 7·55 and is soluble in sodium hydrogen carbonate. When curacin is treated with diazomethane, a mono methylcuracin is produced which fails to give the Millon reaction and is insoluble in 0·1 N sodium hydroxide.

Curacin has been found to be an ester of an aromatic acid $C_9H_8Cl_2O_4$, identified as dichloroisoeverninic acid (I), with a carbohydrate-like substance, which is responsible for the positive Molisch, Fehling and iodoform tests. The reaction with tetrazolium salts is negative.

The ester linkage of dichloroisoeverninic acid to the carbohydrate is very sensitive to alkali. Treatment of curacin with aqueous 0·1 N sodium hydroxide at 100° for 5 min or for 24 hr at room temperature hydrolyzes the ester and dichloroisoeverninic acid can be obtained in quantitative yield by acidification and extraction with ether.

The aqueous solution containing the carbohydrate failed to yield any recognizable products.

This hydrolysis can be followed very easily by U.V.-spectrophotometry, because curacin in 0·1 N sodium hydroxide, exhibits in its U.V.-spectrum an intense peak at 294 mμ (ε 7800), which after 24 hr at room temperature has shifted to 300 mμ (ε 4700), the absorption characteristic of dichloroisoeverninic acid under the same conditions. (λ_{max} 300 mμ; ε 4750) (Fig. 1).

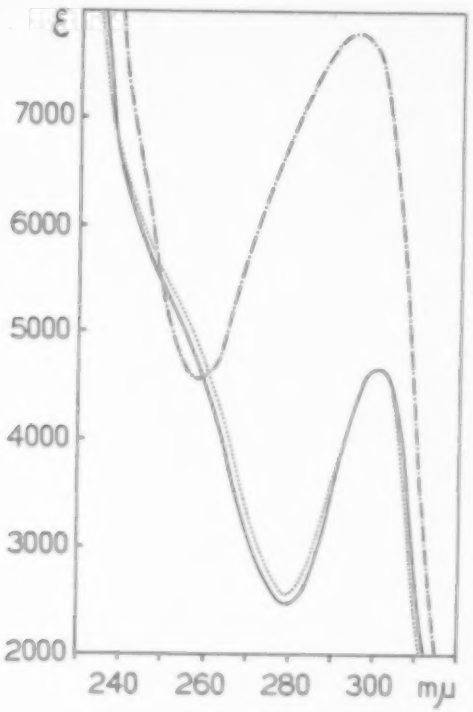


FIG. 1. U.V.-Spectra in 0·1 N sodium hydroxide.
– – – – – Curacin (After 6 min)
. . . . . Curacin (After 24 hr)
——— Dichloroisoeverninic acid.

It is interesting to note that the hydroxamic acid test for esters is negative with curacin and methyl-curacin, but this seems to be the rule with heavily substituted benzoic acids.[1]

Curamycin in 96 per cent ethanol shows λ_{max} 284 mμ ($E^{1\%}_{1cm}$ 9·9) and from this figure and the identity of absorption of curacin in the same solvent (λ_{max} 284 mμ, ε 7400) (Fig. 2), a molecular weight of about 1360 can be calculated for the antibiotic, in fair agreement with that obtained from analytical and degradation data. From the U.V. spectra of curamycin and curacin it is evident that the dichloroisoeverninic acid is the only chromophoric group present.

If from curacin, $C_{15}H_{18}Cl_2O_7$, the dichloroisoeverninic acid residue, $C_9H_6Cl_2O_3$, is

[1] F. M. Dean, J. C. Roberts and A. Robertson, *J. Chem. Soc.* 1432 (1954).

deducted, there remains a residue $C_6H_{12}O_4$, that corresponds to the carbohydrate component. This moiety has not yet been isolated either as such or in form of a derivative, as it is decomposed during the alkaline hydrolysis. The formula $C_6H_{12}O_4$ and the positive iodoform test indicate that the carbohydrate-like compound is a di-desoxyaldohexose containing the grouping (CH_3-CHOH—). That it is an aldose follows from the fact that curacin contains a carbonyl group (semicarbazone, *p*-tosyl-hydrazone and dinitrophenylhydrazone) which can be titrated as an aldehyde according to Willstätter–Schüdel.

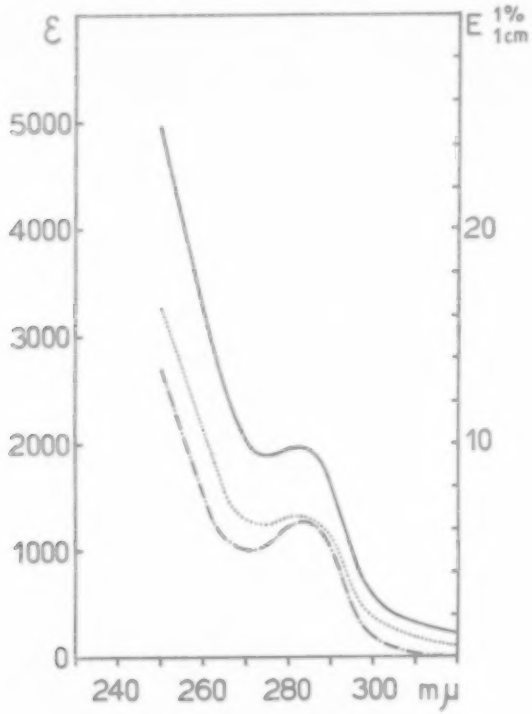


FIG. 2. U.V.-Spectra in 96% ethanol.
——— Curamycin (calc. $E^{1\%}_{1cm}$)
. . . . . Curacin
–·–·–·– Dichloroisoeverninic acid.

This carbonyl group can be reduced with sodium borohydride. In the resulting dihydrocuracin the ester linkage is more stable than in curacin. It is necessary to boil dihydrocuracin with 0·1 N sodium hydroxide for 100 min, to effect complete hydrolysis, whereas 5 min boiling suffices in the case of curacin.

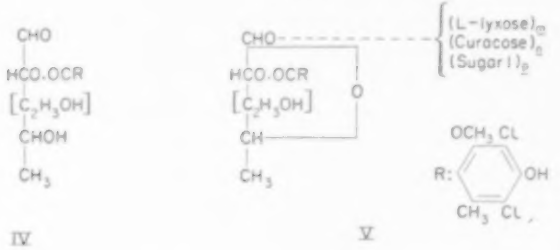
Curacin on acetylation yields a tri-acetyl derivative. Since one of the acetyl groups must reside on the phenolic group of the dichloroisoeverninic acid residue, two acylatable hydroxyl groups must be present in the carbohydrate compound. One of these must be hemiacetalic because triacetylcuracin does not give an immediate positive Fehling reaction. This is also in agreement with the fact that curacin and

methyl-curacin, in contradiction to dihydrocuracin and triacetylcuracin, show mutarotation.

Since neither curacin nor dihydrocuracin consume periodic acid under the usual conditions of oxidation, it is clear that the two non-phenolic hydroxyls present in curacin are not located at vicinal carbon atoms. Furthermore structures in which the carbon atom next to the carbonyl contains a free hydroxyl group are excluded by these results.

In the solid state curacin seems to have at least in part an aldehyde structure as its IR-spectrum in potassium bromide shows a band at 1730 cm^{-1} (ester carbonyl) as well as one at 1709 cm^{-1} that can only be attributed to an aldehydo group.

III



IV V

That the aromatic acid, $C_9H_8Cl_2O_4$, obtained from curacin, was dichloroisoeverninic acid followed from its conversion by catalytic reduction, with Raney-Nickel as catalyst, to isoeverninic acid (II), which was identified by direct comparison with an authentic sample. Dichloroisoeverninic acid could also be obtained by treatment of curamycin with alkali.

Alkaline hydrolysis of methyl-curacin and methyl-curamycin furnished dichloro-O-dimethylorsellinic acid (III), which could be also prepared by the action of diazomethane on dichloro-isoeverninic acid and subsequent saponification.

Dichloroisoeverninic acid has not been found in nature in the free state. A pattern of substitution similar to that of dichloroisoeverninic acid is found in one of the benzene rings of some natural occurring depsidones, such as the chlorine containing compounds from lichens gangaleodine, diploicine[2] and vicanicin[3] and in the antibiotics of the nidulin group.[1] In both cases, the carboxyl contributes to the formation of a depside and the *ortho* hydroxyl participates in ether formation with a phenyl group, instead of with methyl as in isoeverninic acid.

From these data, a preliminary partial structure for curacin (IV) can be deduced. It is based in the reasonable hypothesis that the aldehydo group, by enhancing the electrophilic activity of the carbonyl of the dichloroisoeverninic acid residue, facilitates the hydrolysis of curacin by alkali and that the absence of this group in dihydrocuracin

[1] T. J. Nolan and J. Keane, *Proc. Roy. Soc. Dublin* **22**, 199 (1940); V. E. Davison, J. Keane and T. J. Nolan, *Ibid.* **23**, 143 (1943); T. J. Nolan, J. Algar, E. McCann, W. A. Manahan and N. Nolan, *Ibid.* **24**, 319 (1948).

[2] S. Neelakantan, T. R. Seshadri and S. S. Subramanian, *Tetrahedron Letters* No. 9, 1 (1959).

is cause of its greater resistance to hydrolysis. The grouping (C_2H_3OH) may or may not be branched, the only condition being that the two remaining hydroxyls cannot be located at neighboring carbon atoms and that the terminal methyl adjoins a carbon carrying a hydroxyl group (iodoform test). Hemiacetal formation between the carbonyl and one of the hydroxyls as exemplified in V will explain the mutarrotation.

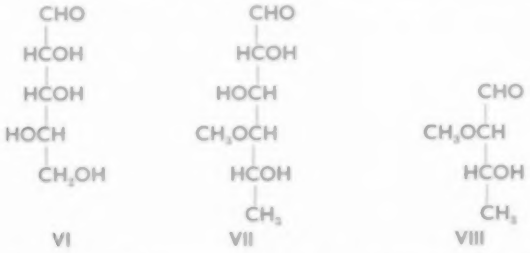
It is doubtful that curacin contains a 2-deoxy aldose sugar, because the Dische and the xanthydrol reactions are negative, although the possibility that this is due to constitutional features in the molecule cannot be dismissed.

When the material remaining in solution after the separation of curacin from the hydrolysis of curamycin was subjected to further treatment with 0·1 N hydrochloric acid and then to paper chromatography, the presence of three different substances which reacted with the usual carbohydrate reagents could be demonstrated. Preparative separation of the three components could be effected by chromatography on a cellulose column.

The substance first eluted from the column could not be crystallized, either as such or in form of derivatives and was set aside for future work. As it gives some carbohydrate reactions, it is provisionally designated sugar 1. The component in the following eluate crystallized readily and was found to be the unknown 4-O-methyl-D-fucose (VII) named by us D-curacose.

The sugar eluted with the last fractions was only obtained as a syrup. It was identified as L-lyxose (VI) by the observation that it gave an osazone m.p. 163°, identical with L-xylosazone, which when mixed with D-xylosazone melted at 205°, the m.p. reported for DL-xylosazone. The *p*-bromophenylhydrazone had the same m.p. and rotation, except for the opposite sign, as the derivative from D-lyxose. The behavior of the sugar on ionophoresis was identical to that of D-lyxose and different from the other pentoses.

This is the first time that L-lyxose (VI) has been found in a natural product, although other sugars configurationally analogous to it have been isolated from certain antibiotics. Streptose, oxystreptose and novobiose have three asymmetric carbon atoms corresponding sterically to the three central carbon atoms of L-lyxose.



The sugar $C_7H_{14}O_5$ having intermediate mobility contained one C-methyl and one methoxy group. When it was treated with hydrobromic acid according to Hough *et al.*[4] and the reaction products were submitted to paper chromatography, a faint spot with an R_f identical to that of L-fucose was observed. When larger amounts of curacose became available a fully methylated derivative could be prepared. This crystalline compound was found identical, except for the sign of rotation, with α-methyl-2,3,4-O-trimethyl-L-fucoside, prepared from L-fucose in the same manner.

[4] L. Hough, J. K. N. Jones and W. H. Wadman, *J. Chem. Soc.* 1702 (1950).

This confirmed that D-curacose was an O-methyl-D-fucose. The known 2- and 3-O-methyl ethers of D- and L-fucose differ from curacose in their m.p.s and rotation (Table 1) and behavior on paper chromatography. D-Curacose is not 5-O-methyl-D-fucose, because the methylated methyl glycoside prepared from it has a pyranose structure, and it follows that it must be 4-O-methyl-D-fucose (VII).

Another methyl ether of D-fucose found in nature is the well known digitalose (3-O-methyl-D-fucose), but the 4-methyl-ether has never been isolated before. It is interesting also to note that the methylation of the 4-hydroxyl group could not be effected by Gardiner and Percival[5] by incomplete methylation of methyl-α-L-fucopyranoside.

When curacose is oxidized with an excess of sodium periodate at pH 3·6, the consumption of the reagent is completed in 2 hr with 2 moles of periodic acid reduced and one mole of formic acid produced. This seems to be a case similar to the oxidation of L-fucose described by Hough *et al.*[6] who found that the sugar consumed rapidly 3 moles of the reagent, forming a rather stable formyl ester of lactaldehyde. In our case a 3-formyl ester of 2-O-methyl-D-threose (VIII) should be formed, which explains why only 1 mole of formic acid is detected.

Curacose is dextrorotatory and does not mutarotate. It is interesting that all the known ethers of D-fucose are dextrorotatory (Table 1).

TABLE 1. MONO-O-METHYL ETHERS OF D- AND L-FUCOSE

Substances	M.p.	$[\alpha]_D$ (H_2O)	Reference
2-O-Methyl-D-fucose	155°; 161°	+73° → +87°	*a*
2-O-Methyl-L-fucose	151°	−87·2°	*b*
3-O-Methyl-D-fucose (D-digitalose)	119°	+106°	*c*
3-O-Methyl-L-fucose	109°; 110°	−97°	*b*
4-O-Methyl-D-fucose (D-curacose)	131°; 132°	+82°	

a H. B. MacPhillamy and R. C. Elderfield, *J. Org. Chem.* 4, 150 (1939).
b J. G. Gardiner and E. Percival, *J. Chem. Soc.* 1414 (1958).
c J. D. Lamb and S. Smith, *J. Chem. Soc.* 442 (1936).

It is evident that in curamycin, the curacin moiety (IV) is linked glycosidically to an oligosaccharide of a molecular weight about 1000, formed by several molecules of L-lyxose, D-curacose and sugar 1. It does not reduce Fehling reagent and hence cannot contain a free carbonyl group. Schematically curamycin structure can be represented shown in V, where *m*, *n* and *p* are the number of molecules of each individual sugar present in the oligosaccharide.

EXPERIMENTAL

M.p.s are not corrected. pK^*_{MCS} were determined in methylcellosolve-water (80:20 by weight).

Streptomyces cura-coi was grown in a medium containing 3% (by weight) of cotton seed meal, 5% corn starch, 0·015% protein hydrolyzate, 0·5% sodium chloride, 0·2% calcium carbonate and water added to complete 100 parts in volume.

Preparation of curamycin

Ten liters of harvested broth, with a content of 155 mg of curamycin per liter (based on biological potency), were adjusted to pH 9·5 with 40% sodium hydroxide solution, 900 g filter aid added, the

[5] J. G. Gardiner and E. Percival, *J. Chem. Soc.* 1416 (1958).
[6] L. Hough, T. J. Taylor, G. H. S. Thomas and B. M. Woods, *J. Chem. Soc.* 1213 (1958).

mycelium filtered and the cake washed with 1 liter of water three times. The filtrate and washings were adjusted to pH 7·0 with 10% hydrochloric acid and extracted twice with 2500 ml of ethyl acetate, the activity passing into the solvent. The extracts were concentrated in vacuum to 500 ml, the concentrate was washed with 250 ml water. After addition of 5 g of decolorizing charcoal added to the ethyl acetate layer and filtration, the solution was concentrated to 30 ml. On standing overnight at 5°, the curamycin precipitated in crystalline form (930 mg, m.p. 196–198°). It was recrystallized by dissolving it in a minimum amount of boiling ethanol (98%) and adding after cooling four volumes of petroleum ether (b.p. 69–72°) and one volume of absolute ethyl ether (m.p. 198°). For analysis the material was recrystallized several times from isopropyl alcohol and then from ethyl acetate. Needles, m.p. 198°, $[\alpha]_D$ −5·3° (*c*, 1; chloroform); −5·0° (*c*, 1·0; pyridine); no mutarrotation. λ_{max} 284 mμ, $E^{1\%}_{1cm}$ 9·9. pK^*_{MCS} 7·48 (Found: C, 48·85, 49·12; H, 6·45, 6·49; Cl, 4·67, 5·05; OCH_3, 8·85; (C) CH_3, 9·38. $C_{53}H_{84}Cl_2O_{22}$ (1301) requires C, 48·89; H, 6·30; Cl, 5·45; $4OCH_3$, 9·53; 8 (C)CH_3, 9·22. $C_{55}H_{86}Cl_2O_{23}$(1345) requires C, 48·89; H, 6·30; Cl, 5·45; $4OCH_3$, 9·53; 8(C) CH_3, 9·22 C_{55}-$H_{86}Cl_2O_{23}$ (1345) requires C, 49·06; H, 6·38; Cl, 5·27; $4OCH_3$, 8·99; 8 (C)CH_3, 8·90%).

Curamycin is easily soluble in acetone, chloroform, acetic acid and pyridine; less so in methanol, ethanol, isopropyl alcohol and butyl acetate; almost insoluble in water, ether and benzene. Curamycin gives a positive Molisch, anthrone and furfural reactions; Fehling and Tollens tests are negative. It gives a positive Millon's test for phenols, although other phenolic reactions are negative (Folin, ferric chloride). A positive iodoform test is obtained.

Methyl curamycin

Three hundred milligrams of curamycin were dissolved in a mixture of 7 ml ethanol and 7 ml ethyl acetate. An excess of diazomethane in ether was added and the solution left at 5° for 72 hr. The solvents were then evaporated to dryness and the solid, partially crystalline, residue, was recrystallized from 5 ml ethanol. 283 mg of *methyl curamycin* were collected by filtration. Needles, m.p. 224°, unchanged by further crystallization. $(\alpha)_D$ +6·6 (*c*, 1·21, pyridine). The substance was purified for analysis by repeated recrystallization from benzene. (Found: C, 49·97, 50·37; H, 6·45, 6·34; Cl, 5·50, 5·33; OCH_3, 11·59. $C_{54}H_{84}Cl_2O_{22}$ (1315) requires: C, 49·26; H, 6·38; Cl, 5·39; $5OCH_3$, 11·78. $C_{56}H_{88}Cl_2O_{23}$ (1359) requires: C, 49·44; H, 6·47; Cl, 5·22; $5OCH_3$, 11·40%).

Methyl curamycin is easily soluble in acetone, chloroform, acetic acid, pyridine and ether and less soluble in methanol, ethanol, with a low solubility in benzene. It gives the same reactions as curamycin, except for the Millon's reaction, which is negative.

Mild acid hydrolysis of curamycin

(a) *Curacin.* One gram of curamycin was suspended in 100 ml 0·1 N hydrochloric acid and the solution was heated in a boiling water bath, with good agitation, for 30 min. The solid dissolved slowly and when the heating was finished, a clear, light yellow solution was obtained. It was filtered hot to eliminate a very small amount of insoluble dark products. On cooling a crystalline precipitate began to appear that after standing overnight at 5° was filtered. Yield: 267 mg, m.p. 138–140°. Recrystallized several times from chloroform, irregular plates, m.p. 145°, $[\alpha]_D$ +41·3° → +21·3 (20 hr) (*c*, 1·0, pyridine). pK^*_{MCS} 7·55. (Found: C, 45·77, 45·78; H, 5·15, 4·85; Cl, 17·93, 18·28; OCH_3, 8·13; (C)CH_3, 10·87; −CHO, 0·96. $C_{15}H_{15}Cl_2O_7$ requires: C, 45·33; H, 4·53; Cl, 17·88; $1OCH_3$, 7·83; 2 (C)CH_3, 7·55%).

Curacin is very soluble in methanol, ethanol and acetone; less so in chloroform and benzene, sparingly soluble in ethyl ether and water. It is soluble in sodium hydrogen carbonate solution. It gives a positive Molisch, Tollens, Fehling, Millon and Folin (phenol) reaction and a positive iodoform test. The ferric chloride test is negative.

(b) *Carbohydrate fraction.* The mother liquors from the filtration of curacin, which give a strong Molisch and Fehling test, were treated with Amberlite IR 4B until the solution was free of chlorine ions, concentrated in vacuum to a small volume and freeze dried. 658 mg of a vitreous yellow product were obtained and employed in the work described further below.

Methylcuracin

500 mg of curacin were suspended in 10 ml ethyl ether and treated with an excess of diazomethane in ether. After 24 hr the clear solution was evaporated and a fresh solution of diazomethane added. The glassy residue obtained on evaporation crystallized by dissolving it in 3 ml of dry benzene

(m.p. 118–119°). For analysis it was recrystallized first from benzene and then from water, m.p. 118–119°: $(\alpha)_D$ +56° → +45° (5 hr) (*c*, 1·0 pyridine). λ_{max} 284 mμ (ε 570) in ethanol. (Found: C, 48·15; H, 5·20; Cl, 17·52; OCH_3, 15·12. $C_{12}H_{20}Cl_2O_7$ requires: C, 48·60; H, 5·08; Cl, 17·97; $2OCH_3$, 15·77%).

Methyl curacin is very soluble in ether, chloroform; less in methanol, ethanol, benzene; soluble in boiling water, poorly soluble in cold water. Millon and Folin reactions are negative. The Molisch, Fehling and Tollens tests are positive. It behaves as a neutral product, consuming no alkali when titrated in 50% ethanol. It is insoluble in 0·1 N sodium hydroxide.

Curacin semicarbazone

One hundred milligrams of curacin were suspended in 5 ml of a water solution containing 500 mg semicarbazide hydrochloride and 750 mg sodium acetate. By heating at 80°, curacin dissolves in about 15 min. On cooling a crystalline precipitate appeared that was filtered and recrystallized from ethanol (prisms, m.p. 168°). It is soluble in saturated sodium hydrogen carbonate solution. (Found: C, 44·13, 44·08; H, 4·87, 4·88; Cl, 16·13; N, 9·37, 9·47. $C_{16}H_{21}Cl_2N_3O_7$ requires: C, 43·83; H, 4·79; Cl, 16·21; N, 9·58%).

Curacin p-*tosylhydrazone*

Five hundred milligrams of curacin and 500 mg of *p*-tosylhydrazide were suspended in 30 ml ethanol and refluxed for 30 min. A clear solution was obtained that on cooling yielded long needles, that were filtered and recrystallized from methanol, m.p. 176°. It is soluble in 0·1 sodium hydroxide, insoluble in sodium hydrogen carbonate and sodium carbonate. (Found: C, 47·72; N, 4·83; Cl, 12·85; N, 5·59; S, 6·08. $C_{22}H_{26}Cl_2N_2O_9S$ requires: C, 48·05; H, 4·91; Cl, 12·93; N, 5·10; S, 5·84%.)

Curacin dinitrophenylhydrazide

Twenty milligrams of curacin were treated with the usual acidic dinitrophenyl hydrazine–ethanol reagent and heated in a boiling water bath for 2 min. On cooling, a gummy precipitate was formed, which when separated and treated with 50% ethanol, solidified. On recrystallization from 70% ethanol yellow needles were obtained, m.p. 202–203°. Soluble in 0·1 N sodium hydroxide, insoluble in sodium carbonate. (Found: C, 44·63; H, 3·97; N, 10·53. $C_{21}H_{22}Cl_2N_4O_{10}$ requires: C, 44·90; H, 3·90; N, 9·98%).

Dihydrocuracin

Two hundred milligrams of curacin were dissolved in 20 ml of water containing 200 mg of sodium borohydride. After 20 min the solution was acidified to pH 2 with 5 N hydrochloric acid and extracted four times with 10 ml of ethyl ether. The ether was well washed and evaporated to dryness, giving 170 mg of a vitreous solid. It was dissolved in boiling butyl ether and on standing at room temperature and scratching, irregular prisms were collected. After recrystallization from hot butyl ether, the m.p. was 90–93°. $[\alpha]_D^{22} = +17{\cdot}6$ (*c*, 1·0 pyridine, no mutarrotation). λ_{max} 284 mμ (ε 1330). (Found: C, 47·17; H, 5·34; Cl, 18·19. $C_{15}H_{20}Cl_2O_7$ requires: C, 46·99; H, 5·25; Cl, 18·53%.)

Triacetylcuracin

A solution of 800 mg of curacin in 40 ml pyridine and 32 ml acetic anhydride was boiled for 5 min. After cooling the solution was poured into 300 ml of ice-water. The resulting gummy precipitate solidified on addition of fresh cold water. The solid was then collected and well dried, (560 mg). On digestion with a few ml of dry ether it crystallized. On three recrystallizations from the minimum amount of boiling ethanol 400 mg of small short prisms were obtained, m.p. 193–194°. $[\alpha]_D$ +15·8 (*c*, 1·0 pyridine). No change in rotation was detected in 24 hr. λ_{max} 284 mμ (ε 905) in ethanol. (Found: C, 49·71; H, 4·71; Cl, 13·77; CH_3CO, 26·46. $C_{15}H_{15}Cl_2O_7(COCH_3)_3$ requires: C, 49·70; H, 4·14; Cl, 14·00; $3CH_3CO$, 25·44).

Alkaline hydrolysis of curacin. Dichloroisoeverninic acid (I)

One hundred milligrams of curacin were dissolved in 6 ml of 0·1 N sodium hydroxide solution and left for 24 hr at room temperature. After standing, the clear brown yellow solution was acidified to pH 2 with 2 N hydrochloric acid and extracted 3 times with 3 ml of ethyl ether. On evaporation

of the ether a crystalline residue was obtained which when recrystallized from boiling water (Darco) gave 30 mg of prisms, m.p. 129–130°, unchanged by further crystallization. λ_{max} 284 mμ (ε 1270) in ethanol. pK°_{MCS} 5·47; 9·51. (Found: C, 43·30; H, 3·36; Cl, 28·58; OCH_3, 12·60. $C_9H_8Cl_2O_4$ requires: C, 43·15; H, 3·26; Cl, 28·37; 10 CH_3, 12·35%.)

The brown solution remaining after the extraction of dichloroisoeverninic acid gave a strong Fehling reaction. The same results were obtained by boiling the alkaline solution of curacin for 5 min under nitrogen.

Alkaline hydrolysis of dihydrocuracin

A solution of 13 mg of hydrocuracin in 2·6 ml of 0·1 N sodium hydroxide was boiled under nitrogen. Hydrocuracin gradually disappeared and after 100 min the only acidic compound detected was dichloroisoeverninic acid.

The solution was then acidified to pH 2 with hydrochloric acid and the dichloroisoeverninic acid extracted with ether and identified in the usual way (m.p. 129°). The aqueous solution gave a negative Fehling and Molisch reaction. No effort was made to characterize the fraction remaining in solution.

For the control of the hydrolysis, descending chromatography on Whatman No. 1 was employed. The mobile system was the upper phase of a mixture of benzene:acetic acid:water (2:2:1). For development a mixture (1:1) of 1% solutions of potassium ferricyanide and ferric chloride was used.

Isoeverninic acid (II)

One hundred and sixty milligrams of dichloroisoeverninic acid were dissolved in 12 ml of methanolic 1 N potassium hydroxide solution, 5 ml of the usual Raney nickel suspension added and the solution was shaken with hydrogen at 5 atm pressure for 24 hr. After filtering the catalyst, the solution was evaporated to dryness, the residue dissolved in water, acidified to pH 2 and extracted with ether. The ether was washed with water and after drying gave on evaporation 120 mg of small prisms, which after recrystallization from water (Darco), melted at 174–176°. This m.p. was not depressed on admixture of a sample of isoeverninic acid with m.p. 176° prepared by oxydation of acetylisoeverninic aldehyde by an adaptation of the method of Robertson and Stephenson for everninic acid.[7]

Dichloro-O-dimethylorsellinic acid (O-*methyl-dichloroisoeverninic acid*) (III)

Twenty milligrams of the acid melting 129° were dissolved in 4 ml of ethyl ether and an excess of ethereal solution of diazomethane was added. After 48 hr standing in the cold, the ether was evaporated, and the residue refluxed for 1·5 hr in a solution of 2 ml of ethanol and 1·6 ml sodium hydroxide. The alcohol was evaporated in vacuum and the aqueous solution washed with 3 ml ethyl ether, acidified to pH 2 with 20% hydrochloric acid and cooled. White prisms formed which were collected (14 mg), and recrystallized from petroleum ether (b.p. 69–72°) gave a m.p. 135° (Nolan and Murphy),[8] give m.p. 135–136°). pK°_{MCS} 4·91. (Found: C, 45·52; H, 4·02; Cl, 26·48; $C_{10}H_{10}Cl_2O_4$ requires: C, 45·28; H, 3·77; Cl, 26·78%).

Dichloro-O-dimethylorsellinic acid

(a) *From methyl curamycin.* Fifty milligrams of methyl curamycin were suspended in 5 ml 0·1 N hydrochloric acid and heated in a boiling water bath for 30 min. The antibiotic dissolves slowly and a gummy precipitate appeared. After cooling, the water solution was decanted and the precipitate dissolved in ether. The ethereal solution was washed with water, dried and evaporated to dryness. The amorphous residue was heated at 100° for 5 min, with 0·1 N sodium hydroxide. The solution was cooled, acidified with hydrochloric acid and extracted with ethyl ether. On evaporation the ethereal extract gave a solid residue that was recrystallized from petroleum ether boiling 69–72°; it was obtained as long prisms, m.p. 133–134°. It gave no depression in the m.p. when mixed with the acid obtained by methylation of dichloroisoeverninic acid.

(b) *From methyl curacin.* Methyl dichloroisoeverninic acid was obtained by a similar alkaline hydrolysis of methyl curacin, m.p. 135°.

[7] A. Robertson and R. J. Stephenson, *J. Chem. Soc.* 1388 (1932).
[8] T. J. Nolan and D. Murphy, *Proc. Roy. Soc. Dublin* **22**, 315 (1940).

Acid hydrolysis of the carbohydrate fraction

The 658 mg of freeze-dried carbohydrate containing fraction obtained by mild acid hydrolysis of 1 g of curamycin were dissolved in 140 ml of 0·1 N hydrochloric acid and heated in a boiling water bath for 3 hr. The chlorine ions were eliminated by treating batchwise with Amberlite IR4B, the chlorine free solution was concentrated to about 40 ml and finally freeze dried. The material so obtained showed three different spots in papergrams, with R_f's 0·28, 0·52 and 0·59 (descending chromatography, Whatman No. 1, n-butanol:ethanol:water (4:1:5); upper phase was used as mobile phase).

Column chromatography of the hydrolysis products

A column of 18 × 300 mm packed with Whatman Standard Grade Cellulose powder equilibrated with solvent (n-butanol:water, 40:6) was used. Crude hydrolysate (490 mg) in 6 ml of solvent was placed on the top of the column and chromatography carried out as usually. Fractions of about 3 ml were collected and analyzed for the presence of aniline phtalate positive substances. Tubes containing fractions with the same R_f were pooled. As expected, the substance with R_f 0·59 was eluted first, followed by the one with R_f 0·52. Finally that of R_f 0·28 was obtained.

The solutions were evaporated in vacuum, while water was added to eliminate the n-butanol, and then freeze-dried. The amounts recovered were 141 (R_f 0·59); 152 (0·52) and 123 mg (0·28).

Identification of the substance with R_f 0·28 as L-*lyxose* (VI)

The freeze-dried solid was a water clear syrup that could not be crystallized. It reduced Fehling solution and gave a positive Bial test. After several chromatographic trials failed to separate D-lyxose and D-xylose, it was found that ionophoresis with 220 V on Whatman No. 1 impregnated with borate buffer at pH 9·6 during 4 hr, gave a spot (aniline phtalate) that migrated like D-lyxose and was different from the remaining pentoses.[9]

The phenylosazone was prepared in the usual way and melted at 162–163° $[\alpha]_D^{23.5}$ +9·0° → 41·2° (24 hr) (*c*, 0·5 pyridine:ethanol, 1:1). Mixed with a sample of L-xylosazone prepared from L-xylose, with m.p. 182 and $[\alpha]_D^{23.5}$ −8·5° → −42·0° no depression was observed. In mixture with D-xylosazone of m.p. 162°, the m.p. was of 204–205°. Zerner and Waltuch[10] reported a m.p. 205° for DL-xylosazone.

The *p*-bromophenylhydrazone had m.p. 157–158°, $[\alpha]_D^{23.5}$ −30·1° → −10·0° (40 hr) in pyridine. Levene and Timpson[11] give m.p. 155–157° and $[\alpha]_D$ +34·5° → +10·0° (115 hr) for the D-isomer.

The *p*-nitrophenylhydrazone melted at 171° in agreement with Levene and La Forge[12] who gave 169° for D-lyxose *p*-nitrophenylhydrazone.

Identification of the substance with R_f 0·52 as 4-O-*methyl*-D-*fucose* (D-*curacose*)

The freeze-dried material corresponding to the second fraction was crystallized by dissolving in the minimal amount of isopropanol and slowly evaporating at room temperature until crystals appear. The suspension was cooled at 5° overnight and crystallization increased. The crystals were filtered and washed well with cool isopropanol, m.p. 120–122°. On several recrystallizations from ethyl acetate long prisms, m.p. 131–132°, were obtained. $[\alpha]_D^{23.4}$ +82°. No mutarrotation was observed (*c*, 1% water). (Found: C, 46·91; H, 7·89; OCH_3, 17·21. $C_7H_{14}O_5$ requires: C, 47·19; H, 7·86; OCH_3, 17·41.)

D-*Curacose* p-*tosylhydrazone*

Fifty milligrams of curacose and 50 mg of the hydrazide were dissolved in 3 ml of methanol and refluxed for 30 min. On cooling, crystals appeared which were filtered and recrystallized three times from acetonitrile. Long prisms melting at 134° were obtained $[\alpha]_D^{23}$ −16.0° → −3·3° (*c*, 1% pyridine). (Found: C, 48·20; H, 6·34; N, 8·24; S, 9·58; OCH_3, 8·98. $C_{14}H_{22}N_2O_5S$ requires: C, 48·55; H, 6·36; N, 8·09; S, 9·24; 10 CH_3, 8·95%).

Periodate oxidation of curacose

Curacose (8·795 mg) was dissolved in 25 ml of water, 2·5 ml of 0·3 M of sodium metaperiodate added, the volume was brought to 50 ml with water and the solution was allowed to stand at room

[9] R. Consden and W. M. Stanier, *Nature, Lond.* **169**, 783 (1952); M. J. Crumpton, *Ibid.* **180**, 606 (1957).
[10] E. Zerner and R. Waltuch, *Monatsch. Chem.* **34**, 1639 (1913).
[11] P. A. Levene and R. S. Timpson, *J. Biol. Chem.* **115**, 731 (1936).
[12] P. A. Levene and F. B. La Forge, *J. Biol Chem.* **18** 319 (1914).

temperature. Aliquots were taken from time to time and the consumed *meta*-periodate and formic acid produced determined. After 120 min, 1·94 moles of periodate were consumed per mole of sugar and 1·10 moles of formic acid were titrated. A stable state was already reached at that time, because after 240 min the figures were 1·93 moles periodate and 1·18 moles formic acid.

α-Methyl 2,3,4-tri-O-methyl-D-fucopyranoside (methyl-2-3-di-O-methyl-D-curacoside)

A solution of 160 mg of curacose in 9 ml absolute methanol containing 1% hydrochloric acid was refluxed for 6 hr. After elimination of the acid with silver carbonate, the clear filtered solution was evaporated to dryness and the partly crystalline residue was dissolved in 5·5 ml of dimethylformamide and 1·6 ml of methyl iodide. Silver oxide (1·6 g) was added slowly with vigorous stirring, that was continued for 40 hr.[12] The insoluble was separated and washed with dimethylformamide (2 × 2 ml) and chloroform (4 × 4 ml). The washings and the original solution were pooled and washed with 10 ml of 10% sodium cyanide solution in water. The aqueous washing was extracted six times with 5 ml chloroform which was added to the organic phase. Evaporation of the combined extracts yielded 165 mg of a syrup. This material, partly crystalline, well dried, was dissolved in 2 ml of warm petroleum ether (40–60°). On standing at 5° for several days, crystals appeared. They were filtered (50 mg) and recrystallized from petroleum ether several times. Short prisms, m.p. 96–97°; $[\alpha]_D^{23}$ +206° (*c*, 1·0 water).

When mixed with a α-methyl-2,3,4-tri-O-methyl-D-fucoside, m.p. 97°, $[\alpha]_D$ +211° (*c*, 1·0; H_2O), prepared from D-fucose by the method described by Gardiner and Percival[5] for the L-isomer, the product showed no melting point depression. When mixed with the same amount of the L-isomer (m.p. 97°, $[\alpha]_D$ −202°[14] a sharp m.p. 69–70° was observed.

Paper chromatography of mono-O-methyl-fucoses

On descending paper chromatography, employing Whatman No. 1, D-curacose had, with the n-butanol–ethanol–water (4:1:5), mobile phase already described, R_f 0·52 and R_g 0·60, while 2-O-methyl-L-fucose had 0·54 and 0·63 and 3-O-methyl-L-fucose, 0·48 and 0·56. Gardiner and Percival[5] found with the same system 0·56 and 0·60 for the 2-O-methyl isomer and for the 3-O-methyl isomer 0·48 and 0·56.

When benzene–n-butanol–pyridine–water (1:5:3:3) was used as mobile phase the following R_f and R_g were found: D-curacose: 0·56 and 0·66; 2-O-methyl-L-fucose: 0·62 and 0·72; 3-O-methyl-L-fucose: 0·56 and 0·66. Gardiner and Percival[5] found R_f 0·63 for the 2-O-methyl and 0·56 for the 3-O-methyl-L-fucose.

Sugar 1

This amorphous solid gave a positive Molisch reaction and a weak positive Fehling test. Bial, tetrazolium and iodoform reactions were negative. With Dische's reagent for 2-deoxy pentoses, the reaction was a typical (brown-yellow color).

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[12] R. Kuhn, H. Trischmann and I. Löw, *Angew. Chem.* **67**, 32 (1955).
[14] O. Th. Schmidt, W. Mayer and A. Distelmayer, *Liebigs Ann.* **555**, 26 (1944).

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CARBON–CARBON AND CARBON–HYDROGEN BOND ENERGIES AND BOND DISTANCES*

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Abstract—Two types of mathematical relations are discussed, which represent the connection between carbon–carbon bond energies and carbon–carbon bond distances. They similarly describe the relation between carbon-hydrogen bond energies and the corresponding carbon–hydrogen bond distances.

IN a recent communication[1] the suggestion was made that the relation between carbon–carbon bond energies [B(CC), in kcal] and carbon–carbon distances [R(CC) = r, in Å] could be expressed by a power series of the third degree of the reciprocal distances

$$B(CC) = a/r + b/r^2 + c/r^3 \quad (1)$$

and

$$B(CH) = A/\rho + B/\rho^2 + C/\rho^3 \quad (2)$$

where $a = -1140{\cdot}593$, $b = 3252{\cdot}755$ and $c = -1991{\cdot}129$. The corresponding relation between carbon–hydrogen bond energies [B(CH), in kcal] and carbon–hydrogen distances [R(CH) = ρ, in Å] was also considered to be of the same form with the constants: A = 1125·03, B = −2477·006 and C = 1376·444. The authors made the following statement in their paper in reference to the present writer's earlier publications: "We preferred, however, to derive new relations of this kind for CC and CH bonds, since we felt that the published ones were open to criticism".

However, a study of equations (1) and (2) indicates that they have several shortcomings. The most serious difficulty lies in the fact that the summation of the carbon–carbon and carbon–hydrogen bond energies, calculated by means of these equations, does not give the heat of atomization (Qa) for a series of molecules. It is of course a fundamental tenet of bond energy considerations that

$$Qa = l \cdot B_1 + m \cdot B_2 + - - - - \quad (3)$$

where l = number of B_1-bonds, m = number of B_2-bonds, etc.

The heats of atomization are obtained from the usual heats of formation (Qf at 0°K).[2,3] In the case of hydrocarbons the heat of sublimation of graphite [L(C) = 170·4 kcal, at 0°K] and the heat of dissociation of hydrogen [D(H_2) = 103·24 kcal, at 0°K] are also needed.[3] The authors make their calculations at 25°C. This difference in temperature causes only a change of a few kilocalories. The B(CC) and B(CH)

* This research is supported by the U.S. Army Office of Ordnance Research under Contract No. DA-31-124-ORD-10-4.

[1] M. J. S. Dewar and H. N. Schmeising, *Tetrahedron* **5**, 166 (1959).
[2] F. D. Rossini *et al.*, *Selected Values of Properties of Hydrocarbons*. National Bureau of Standards Circular C 461. United States Government Printing Office, Washington, D.C. (1947).
[3] F. D. Rossini *et al.*, *Selected Values of Chemical Thermodynamic Properties*. National Bureau of Standards Circular 500. United States Government Printing Office, Washington, D.C. (1952).

bond energy values reported here were obtained by using equations (3), (4) and (5). These cubic equations were first established in 1958 and are here recalculated.[4]

$$B(CC) = 27{\cdot}00/r - 116{\cdot}00/r^2 + 427{\cdot}533/r^3 \quad (4)$$

and

$$B(CH) = -812{\cdot}61/\rho + 1970{\cdot}90/\rho^2 - 1046{\cdot}71/\rho^3 \quad (5)$$

The numerical values obtained by the use of these equations are shown in Table 1, columns 3 and 6.

TABLE 1.—CARBON–CARBON AND CARBON–HYDROGEN BOND ENERGIES

	R(CC)	B(CC) kcal		R(CH)	B(CH) kcal	
	Å	G	D + S	Å	G	D + S
C_2H_2	1·207[a]	185·7	170·6	1·06[a]	102·0	109·5
C_3	1·28[b]	154·0	—	—	—	—
C_2	1·315[a]	141·5	—	—	—	—
C_2H_4	1·337[c]	134·1	130·4	1·086[c]	99·1	100·5
C_6H_6	1·397[d]	116·7	—	1·090[d]	98·6	—
Graphite	1·421[d]	110·6	—	—	—	—
Graphite	3·354[d]	9·1	—	—	—	—
C_2H_6	1·543[d]	85·2	84·5	1·102[d]	97·0	97·0
Diamond	1·5445[d]	84·9	84·6	—	—	—
CH_4	—	—	—	1·094[d]	98·1	98·2

[a] Ref. 5. [b] Ref. 12. [c] Ref. 7. [d] Ref. 8.

The comparison of the two sets of bond energy values is best done by calculating the heats of atomization for the two cases using equation (3). In Table 2 the experimental values of *Qa* are shown in column 2. The present calculated *Qa*-values

TABLE 2.—HEATS OF ATOMIZATION (*Qa*, kcal)

	Expt.	G	D + S
C_2H_2	389·7	389·7[a]	388·6[b]
C_3	320·8[c]	308·0	—
C_2	141·2[c]	141·5	—
C_2H_4	532·7	530·5	532·5
C_6H_6	1308·1	1293·6	1279·4
Graphite	—	165·9	—
Graphite	—	4·5	—
C_2H_6	667·2	667·0	666·6
Diamond	169·8	169·8	169·8
CH_4	392·9	392·9	392·7

[a] Equations (3–5). [b] Ref. 14. [c] Refs. 10 and 11.

(column 3) naturally check the experimental ones. However, the *Qa*-values derived by Dewar and Schmeising[1] (not mentioned), show differences of several per cent between calculation and experiment.

[4] Presented at the American Chemical Society Regional Meeting, Richmond, Virginia, 5–7 November 1959.

Another discrepancy should be noted. The values for B(CH) as calculated from equation (2), with the appropriate constants given above, must be multiplied by a factor of ten, in order to yield reasonable values. The *Qa*-values for ethane check then satisfactorily. An entirely different set of empirical constants can of course remove this discrepancy as is noted in equations (4) and (5).

The relations between bond energies and bond distances are shown graphically in Fig. 1 and 2. It is seen that the discrepancy in B(CC, C_2H_2) is due to the fact that

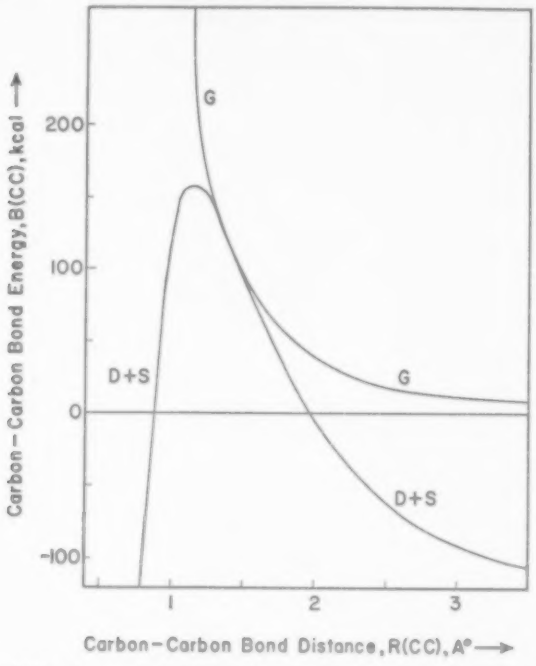

FIG. 1. Relation between carbon–carbon bond energies and carbon–carbon distances. (Equations 1 and 4.)

the cubic relation[1] has a maximum at 1·15 Å or near to R(CC, C_2H_2) = 1·207 Å. It was found during these calculations that the location of a maximum can be shifted by a relatively small change in internuclear distance. The latter are given in Table 1, column 2.[5–8] In the case of ethylene it is likely that Dewar and Schmeising[1] used the internuclear distances given by Bartell and Bonham[9], which are R(CC, C_2H_4) = 1·334 and R(CH, C_2H_4) = 1·085 Å. The corresponding bond energy values B(CC, C_2H_4) = 134·1 and B(CH, C_2H_4) = 103·6 kcal lead to *Qa*(C_2H_4, calc.) = 548·5 kcal, whereas *Qa*(C_2H_4, expt.) = 532·7 kcal. The calculated value is then only 3 per cent greater than the experimental finding.

From Fig. 1 it is seen that the present empirical relation between B(CC) and R(CC), equation (4), includes the interaction energy between the planes in solid

[5] T. L. Cottrell, *The Strengths of Chemical Bonds*. Academic Press, New York (1954).
[6] A. E. Douglas, *Astrophys. J.* **114**, 466 (1951).
[7] J. M. Dowling and B. P. Stoicheff, *Canad. J. Phys.* **37**, 703 (1959).
[8] L. E. Sutton, (Editor), *Tables of Interatomic Distances*. The Chemical Society, London (1958).
[9] L. S. Bartell and R. A. Bonham, *J. Chem. Phys.* **27**, 1414 (1957).

graphite. It is well known that the heat of sublimation of diamond [L(C, dia) = 169·8 kcal = 2 B(CC, dia)]. If the bond energy values in graphite are given by B(CC, 1·421) within the planes and B(CC, 3·354) between the planes, then

$$1{\cdot}5\ \mathrm{B(CC,\ 1{\cdot}421)} + 0{\cdot}5\ \mathrm{B(CC,\ 3{\cdot}354)} = 170{\cdot}4\ \mathrm{kcal} \qquad (6)$$

The cubic relations (equations 4 and 5) include equation (6), whereas relation (1) is not applicable since it gives negative values beyond about R(CC) = 2 Å.

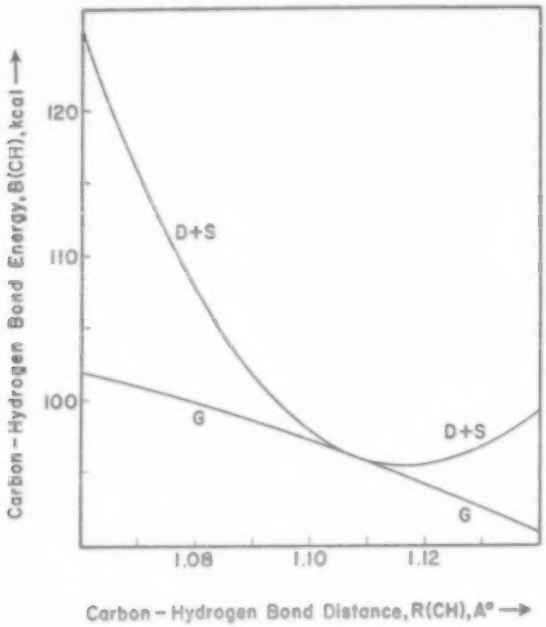

FIG. 2. Relation between carbon–hydrogen bond energies and carbon–hydrogen distances. (Equations 2 and 5.)

The average bond energy of the C_3-molecule from mass-spectroscopy is 160·4 kcal.[10] When calculated from the heat of sublimation of graphite [L(C) = 170·4 kcal], the enthalpy of the C_3-molecule [$\Delta H_0^\circ = 186{\cdot}7 \pm 1{\cdot}5$ kcal (second law) and $188{\cdot}1 \pm 2{\cdot}3$ kcal (third law)]. Pitzer and Clementi[11] give 186·5 kcal. From these values and from the relation

$$3\mathrm{L(C)} - \Delta H_0^\circ = 2\mathrm{B(CC, C_3)} \qquad (7)$$

B(CC, C_3) is found to be 162·0 kcal. From the cubic equation (4), the corresponding distance is found to be 1·26 Å, whereas relation (1) yields no result since the maximum carbon–carbon bond energy is 158·6 kcal at 1·15 Å for this equation. However, Kiess and Broida[12] have lately found the rotational constant for the C_3-molecule to be 0·4280 whence R(CC, C_3) = 1·281 Å. This distance implies B(CC, C_3) = 144·5 kcal from equation (1) and 153·8 kcal from equation (3). Hence a discrepancy exists

[10] J. Drowart, R. P. Burns, G. De Maria and M. J. Inghram, *J. Chem. Phys.* **31**, 1131 (1959).
[11] K. S. Pitzer and E. Clementi, *J. Amer. Chem. Soc.* **81**, 4477 (1959).
[12] N. H. Kiess and H. P. Broida, *Canad. J. Phys.* **34**, 1971 (1956).

in the case of both relations (1) and (3) and depends entirely on the value of the rotational constant (B).

On the other hand, equation (3) yields B(CC, C_2) = 141·5 kcal with R(CC, C_2) = 1·315 Å[13] in good agreement with B(CC, C_2) = 142·9 kcal derived from mass-spectroscopy.[10] The latter value was obtained from the enthalpy of the C_2-molecule [ΔH_0^0 = 195·8 (second law), 198·0 (third law)][10] and 200·0 kcal.[10] The average value is ΔH_0^0 =

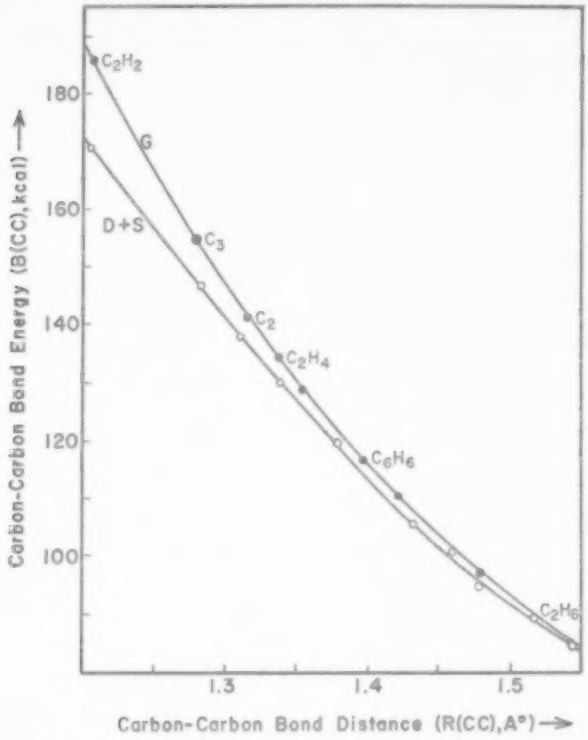

FIG. 3. Relation between carbon–carbon bond energies and carbon–carbon distances. (Equation 4; ref. 14, Tables 6 and 7.)

197·9 kcal. It yields B(CC, C_2) = 142·9 kcal, using L(C) = 170·4 kcal and the relation

$$2L(C) + \Delta H_0^0 = B(CC, C_2) \tag{8}$$

Equation (1) yields 138·0 kcal at R(CC) = 1·315 Å.

Other cubic relations were studied involving small variations of the internuclear distances. They showed no improvement over the case presented here.

In a later communication[14] another relation between the energies and distances of the carbon–carbon bonds is proposed. It is called a tractrix and contains logarithmic terms. These new results are here compared with the present author's cubic as shown in Tables 1 and 2 and Figs. 3 and 4. The two relations now yield comparable values

[13] G. Herzberg, *Molecular Spectra and Molecular Structure. I. Spectra of Diatomic Molecules.* Van Nostrand, New York (1950).
[14] M. J. Dewar and H. N. Schmeising, *Tetrahedron* **11**, 96 (1960).

for the carbon–carbon bond energies from ethane to ethylene, but then the respective curves diverge. It is seen that for acetylene the differences in the bond energies in the two cases are relatively large. When however the C_3 and C_2 molecules are considered it would appear that the higher values of the present cubic equation are the more likely ones.

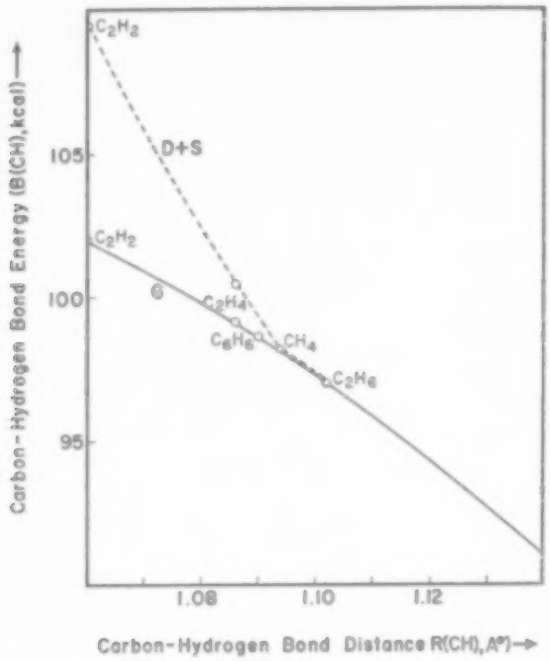

FIG. 4. Relation between carbon–hydrogen bond energies and carbon–hydrogen distances. (Equation 5; ref. 14, Tables 6 and 7.)

It is of interest to note that the heat of atomization of benzene [$Qa(C_6H_6) = 1293{\cdot}6$ kcal; Table 2] when calculated by equations (4) and (5). It is given as 1279·4 kcal by Dewar and Schmeising (Table 7). The respective resonance energies are then 14·5 and 28·7 kcal respectively, since the experimental value of the heat of atomization is 1308·1 kcal. On page 111, ref. 14 it is stated that the true resonance energy of benzene probably lies in the range 5–15 kcal/1 mole.

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SUBSTITUTION IN THE HYDANTOIN RING—I

AMINOMETHYLATION

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Abstract—The behaviour of the hydantoin ring in the aminomethylation reaction was studied in order to determine the orientation of this substitution. It was found that position 3 is the most reactive one and this result is rationalized in terms of influence of structural factors.

Mono-aminomethyl derivatives of hydantoins (I to XV) are described.

CONSIDERING the different positions where an atom or group can be introduced in the hydantoin ring, several papers[1] show that substitution occurs either at the nitrogen in position 1 or in position 3, or at the carbon in position 5. Substitution in N_1 occurs more frequently, for example nitration and formaldehyde in acid medium; the introduction of only one alkyl group results always in substitution at position 3 but these compounds can be further alkylated in position 1;[2] regarding substitution in position 5, it is known that condensation with aldehydes (usually aromatic aldehydes) takes place with the methylene group at C_5.

The simultaneous introduction of two aminomethyl groups was achieved by Bombardieri and Taurins[3] who obtained the 1,3-bis(N-morpholinomethyl)-derivatives by reaction of hydantoin or its 5,5-dimethyl derivatives with formaldehyde and morpholine in yields of 22 and 40 per cent respectively. They also report that the 1,3-bis(N-morpholinomethyl)-derivatives are hydrolysed by acid.

The purpose of this work—by the introduction of the aminomethyl group into only one position of the hydantoin ring—was to determine the orientation of this substitution reaction. The monosubstituted derivatives (I–XV) were prepared from equimolecular amounts of the hydantoin, the secondary amine and formaldehyde in yields of 63–100 per cent except for compound V, the yield in this case being only 31 per cent.

The former approach for solving the structure of the mono-aminomethyl-derivatives was by means of the Stuckey's spectroscopic method.[4] According to this method hydantoins with hydrogen on the nitrogen in position 3 show a bathochromic displacement in the ultra-violet region and an increase in intensity of absorption when changing from neutral or acid medium to an alkaline one. Generally, instead of the end absorption that hydantoins present in neutral or acid medium, there is an appearance of a maximum in alkaline solution. Using the 1,5,5-trimethylhydantoin it was shown here that the observed maximum is simply a shift of one already present at

[1] E. Ware, *Chem. Rev.* **46**, 403 (1950).
[2] A. Novelli, Z. M. Lugones and P. Velasco, *Anales asoc. quim. Argentina* **30**, 225 (1942).
[3] C. C. Bombardieri and A. Taurins, *Canad. J. Chem.* **33**, 923 (1955).
[4] R. E. Stuckey, *J. Chem. Soc.* 331 (1947).

lower wavelength that he assumed, but could not observe due to limitations of the experimental procedure (Table 1).

The ultra-violet spectra of compounds VIII and X show a maximum at 221 mμ in alkaline medium and only end absorption in neutral solution. These results should indicate that substitution took place at N_1 but this conclusion is invalidated by the following observations: the 3-(N-piperidinomethyl)-1,5,5-trimethylhydantoin (XI) and the 1,3-bis(N-morpholinomethyl)-5,5-dimethylhydantoin (XVI), in which both positions are occupied, show this same type of displacement of their spectra in alkaline medium. In alkaline medium identical spectra are obtained for 3-(N-piperidinomethyl)-1,5,5-trimethylhydantoin (XI) and 1,5,5-trimethylhydantoin (literature[4]: λ_{max} 231 mμ; log ε_{max} 3·91), and similarily the spectra for compounds XVI, VIII and X are coincident.

TABLE 1.—ABSORPTION IN THE ULTRAVIOLET REGION[a]

Compound	Neutral medium λ_{max}	log ε_{max}	Alkaline medium[b] λ_{max}	log ε_{max}
1,5,5-Trimethylhydantoin	214	3·49	229	3·72
X[c]	end absorption		221	3·83
VIII	idem		220	3·82
1,3-Bis(N-morpholinomethyl)-5,5-dimethylhydantoin	idem		221	3·82
3-(N-Piperidinomethyl)-1,5,5-trimethylhydantoin	217	3·50	230	3·73

[a] Solvent: alcohol 50°; λ in mμ
[b] Sodium hydroxide 0·01 N.
[c] In absolute alcohol and alkaline medium with sodium ethoxide the results were coincident.

These facts lead to the definite conclusion that in alkaline solution a fission of the linkage between the hydantoinic nitrogen and the aminomethyl group occurs, thus regenerating the parent hydantoin: 3-(N-piperidinomethyl)-1,5,5-trimethylhydantoin giving the 1,5,5-trimethylhydantoin and the substances XVI, VIII and X affording 5,5-dimethylhydantoin. The values here given for the last three aminomethylderivatives in alkaline medium agree with registered values[4] for the 5,5-dimethylhydantoin (λ_{max} 223 mμ; log ε_{max} 3·88).

This cleavage is very fast since the spectrum registered within four minutes after the addition of the base may be exactly reproduced after 24 hours.

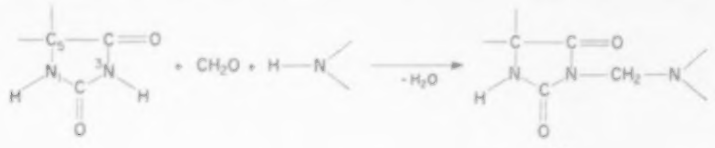
A successful approach to this structural problem is based on comparative methylations of 1,5,5-trimethylhydantoin and 3,5,5-trimethylhydantoin with diazomethane; substitution only being possible at the more acidic N—H in position 3. This reaction affords a new method for distinguishing substitution at positions 1 or 3 of the hydantoin ring, and depends like others (increase of solubility in water by alkali[5] and electrometric titration[6]) on the difference in acidity of the hydrogens in positions 1 and 3; on account of the behaviour of the aminomethyl-derivatives with bases, it is possible to predict that the two methods[5,6] cannot here be applied.

The methylation of the 1,5,5-trimethylhydantoin with diazomethane appears in the literature[7] and the product m.p. 85° described as 1,3,5,5-tetramethylhydantoin must have been impure since the substance obtained either by methylation in the usual

[5] See for example G. P. Lampson and H. O. Singher, *J. Org. Chem.* **21**, 684 (1956).
[6] L. W. Pickett and M. McLean, *J. Amer. Chem. Soc.* **61**, 423 (1939).
[7] H. Biltz and K. Slotta, *J. Prakt. Chem.* **113**, 233 (1926).

way (methyl iodide in alkaline medium) or with diazomethane melts at 106–106·5°. This compound does not show the N—H band in the infra-red present in the starting hydantoin (KBr: 3·21 μ; Nujol: 3·22 μ) and the methoxyl analysis, being zero, indicates beyond doubt that the compound is the 1,3,5,5-tetramethylhydantoin.

Since VI, VIII, X and XII cannot be methylated with diazomethane it is concluded that *the aminomethyl group in these compounds is situated at* N–3 *position.*



(A)

Further evidence supporting this conclusion is provided by comparison of the easiness of reaction with appropriately substituted hydantoins (Table 2). The 1-methylderivatives of hydantoins (1,5,5-trimethylhydantoin and 1-methyl-5,5-pentamethylenehydantoin), react at 20° with morpholine or piperidine (and formaldehyde) producing in very high yields (74 to 91 per cent) the expected products. Applying the same conditions to the isomers methylated in N_3 (3,5,5-trimethylhydantoin and 3-methyl-5,5-pentamethylenehydantoin) the starting compounds are recovered quantitatively or in good yield.

TABLE 2.—EASE OF FORMING MONO-AMINOMETHYLDERIVATIVES

Starting hydantoin	Morpholine		Piperidine	
	% isolated product	% recovered hydantoin	% isolated product	% recovered hydantoin
3-Methyl-[c]	28	59		
1,5,5-Trimethyl-	79		91	
3,5,5-Trimethyl-		85[b]		45
1-Methyl-5,5-pentamethylene-	74		74	
3-Methyl-5,5-pentamethylene-		100		100
Hydantoin[a] (unsubstituted)	75			
5,5-Dimethyl-	100		67	
5,5-Pentamethylene-	97		83	

[a] in dilute solution; [b] 95% in dilute solution.

The parent hydantoins with no substituent on the nitrogen atoms afford the mono-aminomethylderivatives in good yields and these compounds are, therefore, regarded as N–3-derivatives(A). Comparing hydantoin itself and its 3-methyl-derivative (in more dilute solution than for the preceding comparisons) similar results were obtained (Table 2).

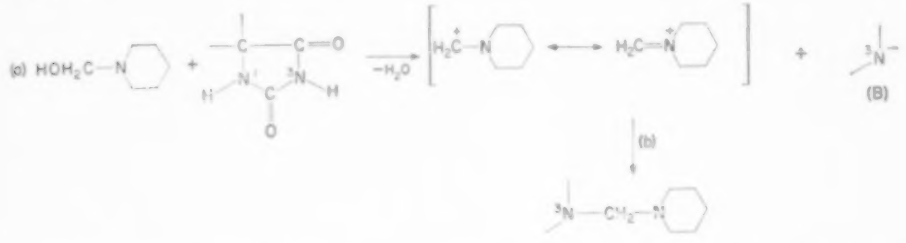
Several attempts at acetylating VIII to transform it into the 1-acetyl-3-(N-morpholinomethyl)-5,5-dimethylhydantoin(IV) and looking for further structural evidence were unsuccessful.

The mechanism of aminomethylation reactions have been extensively discussed by Hellmann and Opitz[8] who assign to the carbonium-immonium ion (originated

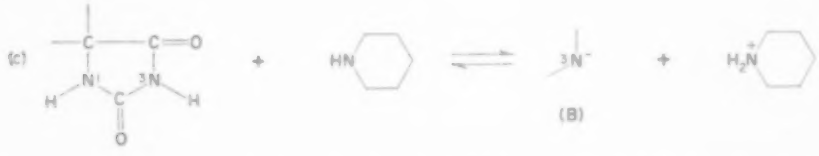
[8] H. Hellmann and G. Opitz, *Angew. Chem.* **68**, 265 (1956).

from formaldehyde, secondary amine and a proton) primordial importance as aminomethylating agent. On the other hand Zinner *et al.*[9] point out that the formation of N-aminomethylderivatives may occur through this same path or by initial reaction between formaldehyde and the "acidic" component N—H, and they give experimental data supporting that the hydroximethylbenzazole is an intermediate in the aminomethylation of benzazoles with secondary amines.

Considering either mechanism it can be explained why the N_3—H is more reactive than the N_1—H under the conditions studied. After the hydroximethylderivative of the secondary amine is formed, the carbonium-immonium ion will be originated (a) reacting N_3—H predominantly because its acid dissociation constant (pK_a 9·12 for the hydantoin[10]) is much higher than that of N_1—H (pK_a 14 or more[6]); the hydantoin anion (B) that leads to the final product according to (b) being formed at the same time.



If instead the reaction starts with nucleophilic attack on the formaldehyde by the "acidic" component N—H, the most reactive part will also be N_3—H since according to the procedure used the equilibrium (c) is first established wherein position 3 will participate prevailing over position 1, and hence the hydantoin anion (B) will be the one added to the formaldehyde.



Considering either reaction mechanism it could be anticipated that in the presence of one mole of acid the aminomethylation would be made difficult by the opposition of the acid to the dissociation of N_3—H and N_1—H (as mentioned above the whole process leading to the carbonium-immonium ion from the amine and formaldehyde requires a proton): in fact aminomethylation of 5,5-dimethylhydantoin using morpholine hydrochloride instead of the free base, under conditions (65°) in which both nitrogens are attacked, yielded only 5 per cent of compound VIII and 92 per cent of the unreacted hydantoin was recovered.

Other experiments show that for hydantoins substituted at C_5, there are reasons of a steric nature, besides the electronic factors, that make position 3 the easier to react.

[9] H. Zinner and B. Spangenberg, *Chem. Ber.* **91**, 1432 (1958), and references therein cited.
[10] J. K. Wood, *J. Chem. Soc.* **89**, 1831 (1906).

From the 3,5,5-trimethylhydantoin it is possible to obtain the 1-(N-morpholinomethyl)-3,5,5-trimethylhydantoin carrying out the reaction at 65°, but under identical conditions the 3-methyl-5,5-pentamethylenehydantoin does not react. Accordingly, the bis-morpholinomethylderivative in positions 1 and 3 of the 5,5-dimethylhydantoin, already described in the literature,[3] is obtained in good yield under conditions wherein the 5,5-pentamethylenehydantoin is only substituted in position 3 (almost quantitative yield of compound XII) even if the heating is much longer.

By comparison of the results obtained in aminomethylation experiments carried out in dilute solution (Table 2) with 3,5,5-trimethylhydantoin and with 3-methylhydantoin (recovering 95 and 59 per cent of unreacted hydantoin respectively), it is concluded that two methyl groups at C_5 render substitution at N_1 more difficult; their influence must be due on the one hand to steric hindrance and on the other hand to the decreased acidity of N_1—H owing to the exerted inductive effect.

EXPERIMENTAL*

Monoaminomethyl derivatives. The following procedure was generally used. The secondary amine (0·001 mole) was added to a solution of the hydantoin (0·001 mole) in methanol (1 ml) cooled in a water bath (heat is evolved) and to the solution thus obtained formaldehyde (40% aqueous solution, 0·001 mole) was added. After standing 2 hr at room temp the solution was evaporated to dryness in vacuum and benzene was added several times to ensure the removal of all the water from the crude product.

Direct crystallization of the latter furnished the desired derivative except for II and V whose isolation was done as follows.

3-(N-*Piperidinomethyl*)-5-*methyl*-5-*ethylhydantoin*(II). The partly oily crude product was dissolved in benzene and chromatographed† in a column of neutral Woelm alumina (2·5 g) activity II, eluting with the same solvent and taking fractions of 5 ml each. Practically all the product was collected in the first fraction (partly oily) and only a few mg more were obtained from the next fractions using the same solvent, benzene–chloroform and chloroform. Crystallization of the first fraction gave compound II.

1-(N-*Morpholinomethyl*)-3,5,5-*trimethylhydantoin*(V). The crude product was chromatographed (5 g of alumina Woelm, neutral, activity II) using successively benzene, benzene with gradual addition of chloroform and finally chloroform for elution. The benzene eluted fraction after recrystallization afforded compound V; the eluate from benzene–chloroform (9:1 to 1:1) furnished 27 mg of the starting 3,5,5-trimethylhydantoin identified by m.p. and mixed m.p.

In Table 3 data about purification, analysis, etc. of the aminomethylderivatives are given.

Comparisons of reactivities. Hydantoins and their 1 and 3-methyl derivatives were compared in reactions with morpholine and piperidine maintaining the solution in a thermostat and following the general procedure above described; reaction conditions and results are indicated in Tables 2 and 3.

The comparison of the pentamethylenehydantoin derivatives were performed at 65° because at 20° it is not possible to obtain a homogeneous medium since the 5,5-pentamethylenehydantoin and its 3-methyl derivative do not dissolve completely and with the former, the reaction product soon begins to separate.

From the experiments with 3-methyl-5,5-pentamethylenehydantoin and morpholine or piperidine (65°; 6 hr) washing the crude product with hexane, the unreacted hydantoin was recovered quantitatively (m.p. and mixed m.p.) The 3-methyl-5,5-pentametilenehydantoin was prepared by methylation of the parent hydantoin with methyl iodide in alkaline medium working as for the 1,3,5,5-tetramethylhydantoin (see below); yield 60%, m.p. 210–211° (methanol) (literature:[11] m.p. 212–213°).

* The m.p., taken in sealed capillaries, are not corrected; the ultraviolet and infra-red spectra were measured in Cary (Model 11 MS) and Perkin-Elmer (model 21) recording spectrophotometers respectively. The microanalyses were carried out by Dr. A. Bernhardt (Mülheim, Germany).

† The elution of the aminomethyl derivatives should be done quickly to avoid a long contact with the alumina since otherwise with some of these substances considerable decomposition was observed.

[11] H. C. Carrington and W. S. Waring, *J. Chem. Soc.* 354 (1950).

TABLE 3. MONOAMINOMETHYL DERIVATIVES OF HYDANTOINS

Hydantoin derivative	Reaction conditions[a] ml CH_2OH; T°; hr	Purification solvent; m.p.; (yield %)	Analytical sample: m.p.	C	H	N	O
				required % found			
(I)[b] 3-(N-Morpholinomethyl)-5-methyl-5-ethyl $C_{11}H_{19}N_3O_3$		benzene; 146–147° (73)	147–148°	54·75 55·01	7·94 7·91	17·42 17·33	19·89 19·99
(II)[c] 3-(N-Piperidinomethyl)-5-methyl-5-ethyl $C_{12}H_{21}N_3O_2$		benzene–hexane; 127·5–128·5° (63)	130–131°	60·22 60·11	8·85 8·47	17·56 17·33	
(III) 3-(N-Morpholinomethyl)-5-methyl-5-isopropyl $C_{12}H_{21}N_3O_3$		dioxane–hexane; 155·5–156·5° (88)	156–157°	56·44 56·55	8·30 8·34	16·46 16·32	18·80 18·99
(IV)[d] 1-Acetyl-3-(N-morpholinomethyl)-5,5-dimethyl $C_{12}H_{19}N_3O_4$		benzene–hexane; 91–93° (84)	94–96°	53·52 53·59	7·11 7·14	15·61 15·59	23·76 24·05
(V)[e,c] 1-(N-Morpholinomethyl)-3,5,5-trimethyl $C_{11}H_{19}N_3O_3$	65°; 12	benzene–hexane; 76–78° (31)	78–79°	54·75 54·83	7·94 7·84	17·42 17·57	
(VI) 3-(N-Morpholinomethyl) $C_8H_{13}N_3O_3$	6·5; 20°; 1	ethyl acetate; 128–130° (75)	132–133°	48·23 47·91	6·58 6·53	21·09 21·20	24·10 24·44
(VII)[f,g] 1-(N-Morpholinomethyl)-3-methyl $C_9H_{15}N_3O_3$	idem	ethyl acetate–hexane; 101–102° (28)	102–103°	50·69 50·27	7·09 7·29	19·71 19·62	22·51 22·70
(VIII)[h] 3-(N-Morpholinomethyl)-5,5-dimethyl $C_{10}H_{17}N_3O_3$	1; 20°; 1	141–142° (100)	148–149° (benzene)	52·85 53·10	7·54 7·59	18·49 18·42	21·12 21·30
(IX) 3-(N-Morpholinomethyl)-1,5,5-trimethyl $C_{11}H_{19}N_3O_3$	idem	hexane; 73–76° (79)	76–78°	54·75 54·81	7·94 7·92	17·42 17·37	19·89 20·13
(X) 3-(N-Piperidinomethyl)-5,5-dimethyl $C_{11}H_{19}N_3O_2$	idem	hexane; 93–95° (67)	96–98° (dioxane–hexane)	58·64 58·57	8·50 8·65	18·65 18·20	14·21 14·04
(XI) 3-(N-Piperidinomethyl)-1,5,5-trimethyl $C_{12}H_{21}N_3O_2$	idem	hexane; 90·5–94° (91)	94·5–95·5° (AcOEt)	60·22 59·72	8·85 8·84	17·56 17·41	13·37 13·29
(XII)[i] 3-(N-Morpholinomethyl)-5,5-pentamethylene $C_{12}H_{21}N_3O_3$	3; 65°; 1	178–179° (97)	181–182° (dioxane–hexane)	58·40 58·26	7·92 7·96	15·72 15·73	17·96 18·33
(XIII) 3-(N-Morpholinomethyl)-1-methyl-5,5-pentamethylene $C_{14}H_{23}N_3O_3$	idem	hexane; 76–78° (74)	77–78° (AcOEt-hexane)	59·76 59·75	8·24 8·36	14·94 15·01	17·06 17·06
(XIV) 3-(N-Piperidinomethyl)-5,5-pentamethylene $C_{14}H_{23}N_3O_2$	idem	dioxane; 189–193° (84)	191–193° (alcohol)	63·36 63·42	8·74 8·66	15·84 16·05	12·06 12·23
(XV) 3-(N-Piperidinomethyl)-1-methyl-5,5-pentamethylene $C_{15}H_{25}N_3O_2$	idem	hexane; 80–81° (74)	81–81·5°	64·48 64·52	9·02 8·78	15·04 15·28	11·46 11·70

[a] Deviations from the general procedure are specified.
[b] During the reaction crystallized from the solution.
[c] For isolation see text.
[d] Due to the low solubility of the 1-acetyl-5,5-dimethylhydantoin double volume of methanol was used and even so only after addition of formaldehyde a complete solution was obtained.
[e] With 3,5,5-trimethylhydantoin working as for VII, VIII and X, the starting hydantoin (m.p. and mixed m.p.) was recovered in 95, 85 and 45% respectively washing the crude product with hexane; aminomethylderivatives not isolated.
[f] Recrystallization of crude product from 3·5 ml benzene gave 59% of the starting hydantoin identified by m.p. and mixed m.p.; compound VII was obtained after evaporating the mother liquor.
[g] By heating 12 hr at 65° (as for compound V) the same derivative VII was obtained, m.p. 101·5–103° (yield 72%).
[h] Washed with hexane.
[i] Quantitative yield was also obtained using 6 ml methanol, room temperature and stirring.

Aminomethylation using morpholine hydrochloride. To a solution of 5,5-dimethylhydantoin (0·001 mole) and morpholine hydrochloride (0·001 mole) in methanol (1 ml), formaldehyde (solution 40%, 0·001 mole) was added and heated for 12 hr in a bath at 65°. After evaporation to dryness in vacuum, the residue was dissolved in a solution of sodium bicarbonate (0·001 mole) in water (2·5 ml) and then evaporated again under diminished pressure (benzene was added to remove water completely).

The dry residue was extracted with hot benzene (1 ml) which by concentration to a small volume afforded 11 mg (5%) of a compound m.p. 143–147° proved to be identical with compound VIII by mixed m.p.

The material unextracted by benzene was re-extracted with several portions of hot absolute ethanol and upon evaporation of the combined alcoholic extract yielded 0·118 g (92%) of 5,5-dimethylhydantoin, identified by its m.p. and mixed m.p.

Methylations with diazomethane. For these reaction excess of diazomethane in ethereal solution was used (prepared from 0·003 mole of Diazald[12]) and directly distilled into a dioxane solution of 0·001 mole of the substance to be methylated; the final solution was allowed to stand 24 hr in a refrigerator and then evaporated under reduced pressure.

Compounds VI, VIII, X, XII and 3,5,5-trimethylhydantoin were recovered quantitatively and identified by m.p. and mixed m.p.; attempts to methylate X and the 3,5,5-trimethylhydantoin using dichloromethane as solvent and adding 0·0012 mole of the boron trifluoride–ethyl ether complex were also unsuccessful.

Under the conditions indicated formerly, 1,5,5-trimethylhydantoin furnished[7] after recrystallization of the crude product from ethyl ether–hexane 0·110 g (71%) of 1,3,5,5-*tetramethylhydantoin*, m.p. 101–106°, which recrystallized again from ethyl ether provided 68 mg, m.p. 105–106°. (Found: C, 53·84; H, 7·58; N, 17·71; O, 20·31; —OCH_3, 0·00. $C_7H_{12}N_2O_2$ requires: C, 53·81; H, 7·75; N, 17·93; O, 20·48%).

The same substance was obtained by methylation with methyl iodide: a solution of 1,5,5-trimethylhydantoin (0·01 mole) in alcohol (6 ml) containing sodium hydroxide (0·01 mole) was mixed with methyl iodide (0·011 mole) and heated 3 hr at 60° followed by evaporation in vacuum. Extractions of the solid with ethyl ether and concentration gave 0·530 g (34%) of 1,3,5,5-tetramethylhydantoin, m.p. 103–105° which after further recrystallizations from acetone–ethyl ether remained constant at 106–106·5°; there was no depression in the m.p. when mixed with the sample obtained with diazomethane.

Acetylation attempts. The acetylation of VIII following several procedures was unsuccessful. Acetyl chloride in pyridine (at 25° or 65°); in excess of acetic anhydride at 80° or 130°; acetic anhydride and pyridine at 110°; sodium hydride in benzene and subsequent addition of acetyl chloride; ketene in presence of anhydrous sodium acetate,[13] and silver perchlorate and acetyl chloride in nitromethane. It was not possible to obtain the acetylated product and the starting substance (VIII) could be recovered only in some cases and in low yields.

Attempt to obtain the 1,3-*bis*(N-*morpholinomethyl*)-5,5-*pentamethylenehydantoin.* To a solution of 5,5-pentamethylenehydantoin (0·002 mole) in methanol (6 ml) morpholine (0·004 mole) and formaldehyde (solution 40%, 0·004 mole) were added and maintained at 65° during 15 hr (homogeneous medium throughout the heating period). The solvent was removed in vacuum and the residue after washing with 2 ml warm hexane gave 3-(N-morpholinomethyl)-5,5-pentamethylenehydantoin (0·500 g; 94%), m.p. 175–178°, and gave no depression when mixed with the above described specimen XII.

Under identical conditions but using 5,5-dimethylhydantoin and heating 2 hr with subsequent removal of the solvent (in vacuum) a solid was obtained which after recrystallization twice from cyclohexane yielded 0·340 g (52%) of 1,3-bis(N-morpholinomethyl)-5,5-dimethylhydantoin (XVI), m.p. 129–132° which was raised to 134–136° (literature:[8] m.p. 134–134·5°) by recrystallization from hexane. (Found: C, 55·14; H, 7·64. Calc. for $C_{15}H_{26}N_4O_4$: C, 55·19; H, 8·03%).

[12] Th. J. DeBoer and H. J. Backer, *Rec. Trav. Chim.* **73**, 229 (1954).
[13] R. E. Dunbar and W. M. Swenson, *J. Org. Chem.* **23**, 1793 (1958).

Tetrahedron, 1961, Vol. 15, pp. 100 to 110. Pergamon Press Ltd. Printed in Northern Ireland

QUASSIN AND *NEO*QUASSIN[1]

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Abstract—Structure XIX ($R_1 = H$; $R_2 = CH_3$) was derived for quassin on the basis of extensive chemical and physical evidence.

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THE existence of bitter substances in quassia wood (*Quassia amara*) was reported in 1835.[2] Several unsuccessful attempts to purify the chemical constituents culminated, a century later, in their isolation and partial purification by Clark.[3]

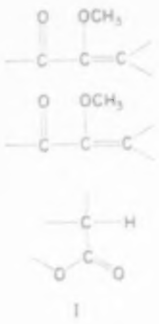
The first extensive investigation of the bitter substances was performed by Robertson and his co-workers[4]. They were able to achieve a clean separation and characterization of the two major constituents, quassin, $C_{22}H_{28}O_6$, and *neo*quassin, $C_{22}H_{30}O_6$, and to define their functionality. Quassin was found to be a lactone, and *neo*quassin the corresponding hemiacetal. The compounds contain two methoxyl groups, at least three C-methyl groups, and no active hydrogen in addition to the hemiacetal hydroxyl group. Acidic degradation indicated the presence of two diosphenol methyl ethers in the molecule.[4c] Acidic hydrolysis of quassin (IR_{max} 1745, 1695, 1680, 1640 cm^{-1}; λ_{max} 255 mμ, ε 11650) yielded norquassin, $C_{21}H_{26}O_6$ (λ_{max} 258 mμ, ε 11200; λ_{max} (KOH) 258 mμ, ε 8200; 312 mμ, ε 3300) which on treatment with diazomethane was reconverted to quassin. Norquassin on treatment with base underwent a benzilic acid rearrangement to give norquassinic acid, $C_{21}H_{28}O_7$ (λ_{max} 259 mμ, ε 9640), which could be further hydrolysed with acid to *iso*bisnorquassinic acid, $C_{20}H_{26}O_7$ (λ_{max} 282 mμ, ε 7910; λ_{max} (KOH) 340 mμ, ε 6000). The last step could be reversed by treatment with dimethylsulphate. It is clear from the above evidence that neither of the acidic reactions involved a skeletal rearrangement and, on that basis, the spectroscopic properties of the nor-compounds provide a strong indication of the presence of two methylated diosphenols in quassin.

The hemiacetal ring of *neo*quassin was further defined by a reaction with acetic anhydride, which yielded anhydro*neo*quassin, $C_{22}H_{28}O_5$, a cyclic enol-ether.[4c] This fact was established by the reformation of *neo*quassin on treatment with aqueous acetic acid. According to the ultraviolet spectra, the newly formed double-bond of anhydro*neo*quassin is not conjugated with either one of the diosphenol methyl ethers.

The quoted results of Robertson *et al.* can be summarized by the partial structure I for quassin. On the basis of infrared evidence, the two ketones and the lactone are situated in six-membered (or larger) rings.

[1] For a preliminary report, see Z. Valenta, A. H. Gray, S. Papadopoulos and C. Podešva, *Tetrahedron Letters* No. 20, 25 (1960).
[2] F. L. Winckler, *Rep. Pharm.* **4**, 85 (1835).
[3] E. P.Clark, *J. Amer. Chem. Soc.* **59**, 927, 2511 (1937).
[4a] E. London, A. Robertson and H. Worthington, *J. Chem. Soc.* 3431 (1950); [b] R. J. S. Beer, D. B. G. Jaquiss, A. Robertson and W. E. Savige, *Ibid.* 3672 (1954); [c] K. R. Hanson, D. B. G. Jaquiss, J. A. Lamberton, A. Robertson and W. E. Savige, *Ibid.* 4238 (1954); [d] R. J. S. Beer, K. R. Hanson and A. Robertson, *Ibid.* 3280 (1956); [e] R. J. S. Beer, B. G. Dutton, D. B. G. Jaquiss, A. Robertson and W. E. Savige, *Ibid.* 4850 (1956).

Our own investigation started with the assumption that a molecule with a relatively large number of unsaturated functions must be particularly well suited for an investigation by nuclear magnetic resonance spectroscopy. The spectrum of quassin[5] revealed the presence of one vinylic hydrogen and four C-methyl groups. Of these, two are tertiary (singlets at 8·45 and 8·79 p.p.m.), one secondary (doublet at 8·86), and one (singlet at 8·15 p.p.m.) is situated on a double-bond. Furthermore, the shift of a signal for one hydrogen at 5·70 p.p.m. in quassin to 6·15 p.p.m. in *neo*quassin indicates the secondary nature of the ether oxygen of the lactone ring. The partial formula I for quassin can therefore be extended to II.



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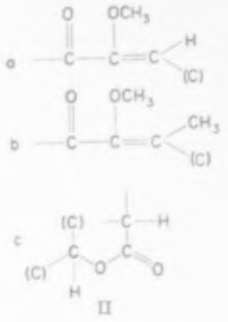

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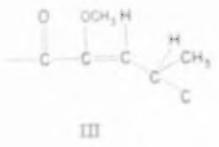

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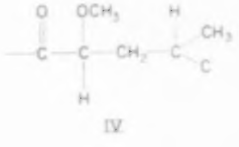

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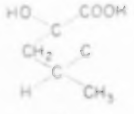

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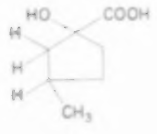

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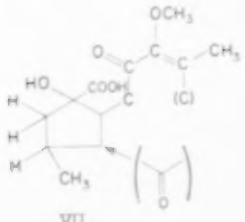


VII

Both quassin and *neo*quassin can be reduced with zinc and acetic acid to the corresponding dihydroderivatives.[4c] On the basis of their NMR spectra, the two dihydrocompounds no longer contain a vinylic hydrogen and the secondary methyl group becomes more shielded during the reduction (a shift of the methyl doublet from 8·86 to 9·10 p.p.m.). This change is best explained by the reduction of III to IV. This postulate was confirmed in the following way. *Neo*quassin and dihydro*neo*quassin were found to be resistant to vigorous treatment with sodium methoxide in methanol; the two compounds were therefore separately treated under similar conditions in CH_3OD. The NMR spectrum of deuterated *neo*quassin shows that the $CHCH_3$ group has been replaced by $CDCH_3$ (triplet at 8·85 p.p.m.) and that one methyl group has

[5] The NMR signals of important compounds are given in Table 1 in the experimental section. For interpretation, see e.g. L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon Press, London, New York (1959).

been completely deuterated (disappearance of the singlet at 8·15 p.p.m.). In contrast, treatment of dihydro*neo*quassin again deuterated one methyl group completely, but left the $CHCH_3$ grouping intact. Since only hydrogens α or vinylogously α to carbonyl groups can be replaced by deuterium under these conditions, partial formulae IIb, III and IV give a satisfactory explanation of these results.[6]

We next turned our attention to the size of the ring containing the grouping III and its position in relation to the remaining oxygen functions. An infrared maximum at 1715 cm^{-1} in the spectra of the dihydrocompounds indicates that the saturated ketone is in a six-membered or larger ring. A definite decision was reached by the investigation of norquassinic acid, the benzilic acid rearrangement product of norquassin.[4c] Since this acid, according to its NMR spectrum, does not contain a vinylic hydrogen, it must be formed by the hydrolysis and rearrangement of the chromophor III and can, therefore, be represented by the partial formula V. Desoxonorquassinic acid,[7] $C_{21}H_{30}O_6$, which must also contain the grouping V, lost the elements of formic acid on treatment with concentrated sulfuric acid, and gave a ketone, $C_{20}H_{28}O_4$, with infrared bands (in $CHCl_3$) at 1740, 1680 and 1645 cm^{-1}. The maximum at 1740 cm^{-1} shows that the newly formed keto-group is in a five-membered ring and the partial formula of norquassinic acid can therefore be extended to VI.

It proved to be relatively easy to establish the relationship of the grouping VI to the remaining diosphenol methyl ether. According to Hanson *et al.*[4e], treatment of norquassinic acid, $C_{21}H_{28}O_7$, with acetic anhydride-sodium acetate yielded a neutral acetate, $C_{23}H_{28}O_7$, with a modified ultraviolet spectrum (λ_{max} 224 mμ, ε 6000; 284 mμ, ε 4200) and infrared bands (in $CHCl_3$) at 1770 and 1740 cm^{-1}. This acetate could be reconverted to norquassinic acid on basic hydrolysis. The compound is clearly the acetate of an enol-lactone and the maximum at 1770 cm^{-1} indicates a 1,5-relationship of the carboxyl and ketone carbon atoms. The partial formula VI can therefore, with some assurance, be extended to VII, since the only other possible extension (see arrow in VII) would lead to a highly strained enol double-bond.

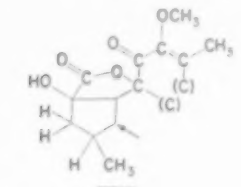
Two additional reactions are of importance for the partial formulation VII. Oxidation of norquassinic acid with lead tetraacetate in acetic acid at room temperature gave a neutral compound, $C_{21}H_{26}O_7$, showing infrared maxima (in $CHCl_3$) at 1785 (γ-lactone), 1735 (lactone), 1670 (unsaturated ketone) and 1630 (double-bond) cm^{-1}. Its NMR spectrum contains signals for all four C-methyl groups, including the $CHCH_3$ group, and shows no hydrogens unshielded by the newly created lactone ring. This high-yield reaction is best explained by an oxidative attack at a position α to the ketone to give VIII, although the attack at one alternate position (see arrow in VIII) cannot be completely excluded.

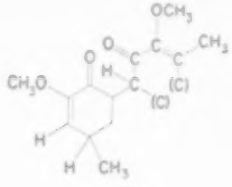
On that basis, quassin can be represented by the partial structure IX, in which the substitution of the two carbons connecting both keto-groups is not rigorously defined. This final point was clarified by the degradation of the desoxodicarboxylic acid (partial formula X, R = H),[7] obtained following the procedure of Beer *et al.*[4d] by the alkaline hydrogen peroxide oxidation of desoxonorquassin. It had been established that one of the carboxyl groups of the diacid is probably tertiary since treatment with methanolic hydrochloric acid gave a monoester, while the corresponding diester,

[6] *Neo*quassin incorporated 5·4 atoms of D, while the value for dihydro*neo*quassin was 6·62 D. Possible reasons for this difference and other deuteration results will be discussed in a separate communication.

[7] Desoxoquassin, $C_{22}H_{30}O_5$, is prepared by the catalytic reduction of anhydro*neo*quassin.[4d] It therefore contains a cyclic ether ring in place of the quassin lactone ring.

prepared with diazomethane, gave a different monoester on prolonged basic hydrolysis.[4d] The monoester X (R = CH_3), $C_{22}H_{32}O_7$, which was found to be stable under the usual decarboxylating conditions, lost the elements of formic acid on treatment with lead tetraacetate in boiling benzene to give a doubly unsaturated ketone, $C_{21}H_{30}O_5$. The NMR spectrum of this ketone shows no vinylic hydrogens and contains methyl singlets at 7·95, 8·16 and 8·94, and a doublet at 9·21 p.p.m. One methyl group must therefore be situated on the newly created double-bond. These data and the modified ultraviolet[8] (λ_{max} 267 mμ infl., ε 6900; 295 mμ, ε 8500) and infrared spectra[9] (I.R.$_{max}$ 1740, ester; 1645, ketone; 1580 cm^{-1}, double-bond) are in good agreement with the partial structure XI for the unsaturated ketone. Since the infrared intensity of the double-bond band is comparable with that of the keto-group, a *cisoid* arrangement of one enone group in XI is indicated.[9,10] This interesting γ-keto acid oxidation can be assumed to proceed through a transition state of the type XII or its non-cyclic equivalent.[10a]


VIII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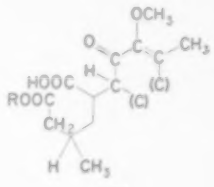
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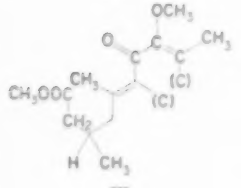
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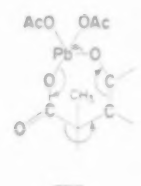
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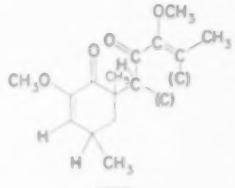
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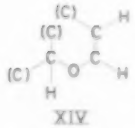
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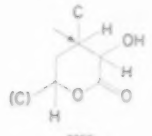
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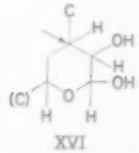

XVI

The chemical and physical properties of the compounds discussed thus lead to the partial structure XIII for quassin and *neo*quassin. It remains to establish the position of the lactone ring and the fourth C-methyl group and to close two carbocyclic rings. An oxidative study of anhydro*neo*quassin completely clarified these structural features. Anhydro*neo*quassin, $C_{22}H_{28}O_5$, is a cyclic enol-ether prepared by the dehydration of

[8] The anomalous ultraviolet spectrum compares with that of the similarly constituted chromophor in diosterol-II: L. F. Fieser, M. Fieser and S. Rajagopalan, *J. Org. Chem.* **13**, 800 (1948).

[9] The unusually low infrared frequency of the keto-group finds its analogy in the spectrum of lactucin: D. H. R. Barton and C. R. Narayanan, *J. Chem. Soc.* 963 (1958).

[10] R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, *J. Amer. Chem. Soc.* **76**, 4013 (1954).

[10a] However, the keto-group need not be mechanistically involved. The formation of olefins on treatment of tertiary carboxyl-groups under comparable conditions has been reported: W. A. Mosher and C. L. Kehr, *J. Amer. Chem. Soc.* **75**, 3172 (1953); L. L. McCoy and A. Zagalo, *J. Org. Chem.* **25**, 824 (1960); G. Büchi, R. E. Erickson and N. Wakabayashi, *J. Amer. Chem. Soc.* In press (G. Büchi, personal communication).

*neo*quassin with acetic anhydride.[4c] In addition to the vinylic hydrogen present in XIII, its NMR spectrum shows two vinylic hydrogens with signals at 3·67 and 5·48 p.p.m. These positions are in good agreement with those of α- and β-hydrogens, respectively, of model enol-ethers. In addition to XIII, anhydro*neo*quassin therefore contains the grouping XIV (*cf.* IIc).

As anticipated, only the strongly nucleophilic enol-ether double-bond was attacked during a mild potassium permanganate oxidation of anhydro*neo*quassin in acetone. Three crystalline products were thus obtained in a high yield: a lactone A, $C_{22}H_{28}O_7$ (I.R.$_{max}$ 1740, 1695, 1685 and 1640 cm^{-1}), its non-lactonic isomer B, $C_{22}H_{28}O_7$ (I.R.$_{max}$ 1695 and 1640 cm^{-1}), and a diol C, $C_{22}H_{30}O_7$. Diol C was converted to compound A on treatment with silver oxide. Oxidation of C with periodic acid gave an amorphous aldehyde-formate which on basic hydrolysis followed by chromium trioxide oxidation yielded a crystalline γ-lactone, $C_{21}H_{26}O_6$ (I.R.$_{max}$ 1775, 1700, 1690 and 1635 cm^{-1}). This degradation, involving the loss of the formate carbon atom, clearly defines the six-membered nature of the oxygen ring in quassin and *neo*quassin. Compounds A and C thus can be represented by partial structures XV and XVI, respectively. The substitution of the carbon atom indicated by the arrow in these formulae was deduced on the basis of the NMR spectrum of the intermediate aldehyde-formate. It contains an aldehyde doublet at 0·31 p.p.m. (J = 6 cycles/sec) and a formate singlet at 2·17 p.p.m; the splitting of the aldehyde peak leaves no doubt about the presence of one hydrogen atom in the α-position.

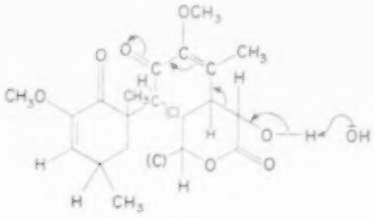
Treatment of lactone A, $C_{22}H_{28}O_7$, with hot aqueous base eliminated two carbon atoms and gave a non-lactonic compound, $C_{20}H_{28}O_5$, with infrared bands (in KBr) at 3450 (OH), 1690, 1660 (unsaturated ketones) and 1630 (double-bonds) cm^{-1}. Partial formulation XVII for lactone A represents the only way in which groupings XIII and XV can be connected, and which at the same time gives a rational explanation of the elimination (see arrows in XVII). The secondary nature of the hydroxyl group in the product of elimination (XVIII), was confirmed by a chromium trioxide oxidation to a ketone, $C_{20}H_{28}O_5$. The absence of any carbonyl maximum above 1715 cm^{-1} in the infrared spectrum of this ketone shows that the newly formed keto-group is located in a six-membered or larger ring.

The complete structure of quassin can now be discussed. The formulation XIX is a unique consequence of all the physical and chemical data described above. On the basis of extensive infrared evidence, ring C cannot be five-membered, and no structure with a seven-membered ring can be constructed which would satisfy all the requirements. The only remaining uncertainty is the position of the fourth methyl group, which can be attached at C_8 or C_9.[11] The sharp NMR singlet corresponding to this methyl group appears at 8·79 p.p.m. in quassin and at 8·94 p.p.m. in *neo*quassin. This shift, associated with the change of the lactone ring to a hemiacetal ring, favors the attachment at C_9.

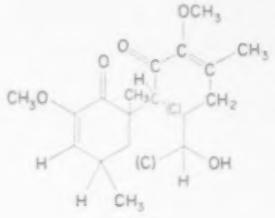
In addition to anhydro*neo*quassin, the treatment of *neo*quassin, $C_{22}H_{30}O_6$, with acetic anhydride–sodium acetate yielded dehydro*neo*quassin (XX), $C_{22}H_{28}O_6$. This unusual dehydrogenation was first reported by Clark[3] and must involve oxidation by air or peroxides. Dehydro*neo*quassin shows infrared bands (in KBr) at 3400, 1697, 1680, 1640 and 1605 cm^{-1} and an ultraviolet maximum at 280 mμ (ε 10500). Oxidation of XX with silver oxide gave dehydroquassin (XXI), $C_{22}H_{26}O_6$, with infrared bands

[11] Only structure XIX ($R_1 = CH_3$; $R_2 = H$) was discussed in our preliminary communication.[1]

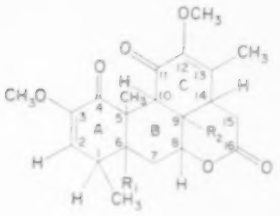
(in KBr) at 1727 (conjugated lactone), 1700, 1690 (ketones), 1635, 1616 and 1590 (double-bonds) cm^{-1}. Ultraviolet maxima at 305 mμ (ε 8600), 268 mμ (ε 7000) and 228 mμ (ε 7000) indicate that one of the chromophores has been extended. The NMR spectra of the two compounds are in good agreement with the assigned structures and again show an unshielding of one methyl group by the lactone ring (singlet at 8·75 p.p.m. in XXI).



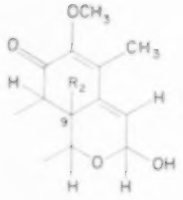
XVII



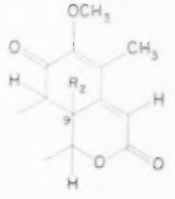
XVIII



XIX



XX



XXI

Clearly, the fact that dehydro*neo*quassin (XX) does not aromatize under the conditions of its formation provides a strong indication that ring C must be blocked. In addition, XX and XXI could not be converted to a phenol on treatment with acid or base, and all attempts to obtain a phenol by a mild dehydrogenation of quassin proved unsuccessful. A vigorous dehydrogenation of quassin with chloranil yielded a small amount of a non-aromatic isomer of XXI. This compelling evidence places the last methyl group at C_9, and the structure of quassin must therefore be XIX ($R_1 = H$, $R_2 = CH_3$).

A surprising confirmation of this assignment came from the study of the previously mentioned compound B, $C_{22}H_{28}O_7$, one of the permanganate oxidation products of anhydro*neo*quassin. The infrared spectrum of a carefully purified sample of B shows the absence of any lactone or unconjugated ketone, while the ultraviolet and NMR spectra exclude the presence of a new double-bond. The compound liberates iodine on treatment with potassium iodide in acetic acid and must therefore contain an

epoxide ring activated by a keto-group. Structure XXII[12] explains the described properties and the following transformations. Treatment of XXII with formic acid in acetone hydrolysed one methoxyl group and gave the yellow compound XXIII, $C_{21}H_{26}O_7$. Its functionality follows from the infrared bands (in KBr) at 3400 (hemiacetal), 1730 (unconjugated ketone), 1690, 1680 (conjugated ketones), 1635 and 1622 (double bonds) cm^{-1}, and from the normal ultraviolet maximum at 264 mμ (ε 9400). The normally very stable methoxyl group in ring C is clearly activated for acid hydrolysis by the epoxide ring as indicated by arrows in XXII.

The hydrolysis of XXIII with methanolic potassium hydroxide yielded the phenol XXIV, $C_{20}H_{24}O_6$. Its NMR spectrum shows the presence of two aldehyde groups (signals at −0·44 and +0·60 p.p.m.), one secondary methyl group (doublet at 9·00 p.p.m.), one tertiary methyl group (singlet at 8·59 p.p.m.), and two strongly and about equally unshielded aromatic methyl groups (7·46 and 7·53 p.p.m.). In agreement with structure XXIV are infrared bands (in KBr) at 3100 (OH), 1715 (aldehyde), 1675 (aromatic aldehyde), 1595 (infl.) and 1583 (aromatic ring), and ultraviolet maxima at 239 mμ (ε 8500) and 296 mμ (ε 8500), shifting to 261 mμ (ε9950) and 314 mμ (ε 5800), respectively, in ethanolic potassium hydroxide. The presence of a hemiketal in ring A follows from the ultraviolet spectrum and from the position of the vinyl hydrogen signal (5·19 p.p.m.).

The aromatization is best rationalized as proceeding through the stages XXIII→XXV→XXVI→XXIV. It was found that no phenol was formed in an alkaline hydrolysis of XXIII in an inert atmosphere. The transformation thus involves an air oxidation which can take place before[13] or after the C_8—C_9 bond-cleavage.

The possibility of an acid catalyzed skeletal rearrangement during the transformation of XXII to XXIV is excluded by the fact that the phenol XXIV was also obtained by the reaction of XXII with sodium metaperiodate and sodium bicarbonate in aqueous methanol followed by basic hydrolysis. These remarkable transformations of the epoxide XXII thus confirm that ring C in quassin is six-membered and that aromatization is possible only after the cleavage of the C_8—C_9 bond. Furthermore, the NMR spectrum of the phenol XXIV reveals the position of the elusive angular methyl group.

The reported formation of 3,4,5-trimethylguaiacol[4b] and 1,2,8-trimethylphenanthrene[4c] in the selenium dehydrogenation of *neo*quassin and its Clemmensen reduction product, respectively, can be easily rationalized on the basis of the proposed structure.

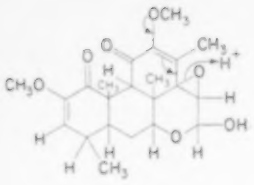
Two fundamentally different biogenetic hypotheses can be formulated for the formation of quassin and *neo*quassin. The compounds could arise from the diterpenoid pimarane skeleton by a series of C-methyl shifts and a shift of a two-carbon fragment. However, the distribution of oxygen atoms and the obvious structural symmetry strongly favor an oxidative coupling of two identical C_{10}-units (XXVII).[14]

The stereochemistry of quassin and additional transformations in the quassin series will be discussed in separate publications.

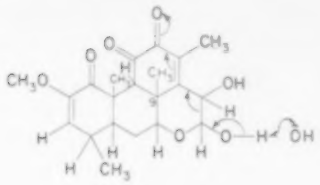
[13] This unusual formation of an epoxide in a permanganate oxidation finds its formal analogy in the well-known epoxidation of α,β-unsaturated ketones with alkaline hydrogen peroxide. The survival of the epoxide is explained by the mild reaction conditions (several minutes in acetone at room temperature).

[13] For air-oxidation of 1,4-diketones to enediones in alkaline solution, *cf.* W. G. Dauben, G. A. Boswell and W. Templeton, *J. Org. Chem.* **25**, 1853 (1960).

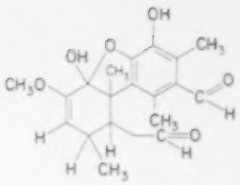
[14] For an authoritative summary on the role of phenol oxidations in biogenesis, see D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll*. Birkhauser Verlag, Basel (1957).



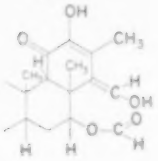
XXII



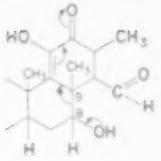
XXIII



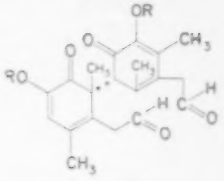
XXIV



XXV



XXVI



XXVII

EXPERIMENTAL

Preparation of pure quassin. Crude quassin supplied by Merck Co. of Canada was found to consist of a mixture of quassin and *neo*quassin. Silver oxide proved to be the most efficient oxidizing agent. The mixture (10 g), m.p. 229°, was dissolved in 200 ml of ethanol and 150 ml of water, and treated with freshly prepared silver oxide (from 40 g of $AgNO_3$) for 15 hr under reflux. The warm reaction mixture was filtered through Celite, the filtrate was diluted with an equal volume of water and extracted with five 50 ml portions of $CHCl_3$. Evaporation yielded a foam (8·3 g) which was purified by a treatment with charcoal in CH_3OH and crystallized from aqueous CH_3OH (total yield 5·8 g); recrystallized product melted at 221°. (Found: C, 67·71; H, 7·28; O, 25·18; C—CH_3, 8·02; OCH_3, 15·81. $C_{22}H_{28}O_6$ requires: C, 68·02; H, 7·26; O, 24·72; 4 C—CH_3, 15·4; 2 OCH_3, 16·0%.)

Preparation of pure neo*quassin*[4a]. "Crude quassin" was treated with aqueous KOH at room temperature, *neo*quassin was extracted with $CHCl_3$ and recrystallized from aqueous CH_3OH, m.p. 231°. Quassin could be recovered from the aqueous solution by saturation with CO_2 and extraction with $CHCl_3$.

Deuteration of neo*quassin.* A solution of *neo*quassin (300 mg) and Na (150 mg) in 6 ml of CH_3OD was heated under reflux for 4 hr. Special precautions were taken to exclude moisture before and during the reaction, which was run under purified and dried N_2. The reaction mixture was poured into $CHCl_3$ (200 ml) and washed with ice-cold aqueous HCl and with ice-water. The solution was evaporated and the residue crystallized from ethyl acetate–pet. ether to give pure product, m.p. 220–222°. Isotopic analysis revealed the presence of 5·4 atoms of D. The same isotopic content was found in a reaction run for 10 hr. Pure *neo*quassin was recovered when CH_3OH was used in place of CH_3OD.

*Deuteration of dihydro*neo*quassin.* Dihydro*neo*quassin acetate was prepared by the reduction of *neo*quassin with Zn and acetic acid.[4c] The acetate (200 mg) was treated with a solution of Na (100 mg) in 6 ml of CH_3OH and refluxed for 5 hr under N_2. The solution was poured into $CHCl_3$ washed with cold aqueous HCl followed by ice-water, evaporated, and the residue crystallized from ethyl acetate to give pure dihydro*neo*quassin, m.p. 204–206°. (Found: C, 66·85; H, 8·50; O, 24·79. $C_{22}H_{32}O_6$ requires: C, 67·16; H, 8·26; O, 24·58%.)

An identical treatment of dihydro*neo*quassin acetate (190 mg) with Na (110 mg) in 6 ml of CH_3OD yielded deuterated dihydro*neo*quassin, m.p. 205–207°, containing 6·62 atoms of D per molecule.

Deformylation of desoxonorquassinic acid. Desoxonorquassinic acid[4d] (100 mg), m.p. 190–194°, was dissolved in 3 ml of conc H_2SO_4 and allowed to stand for 4 hr at room temperature. The solution was extracted with $CHCl_3$. Evaporation yielded a colorless oil (80 mg) which was chromatographed and sublimed for analysis. (Found: C, 72·24; H, 8·43; O, 19·17. $C_{20}H_{28}O_4$ requires: C, 72·26; H, 8·49; O, 19·25%.)

Oxidation of norquassinic acid with lead tetraacetate. Norquassinic acid[4c] (190 mg), m.p. 228–232°, was treated with 200 mg of $Pb(OAc)_4$ in glacial acetic acid (10 ml) for 15 hr at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The

solution was shaken with aqueous $NaHCO_3$ and evaporated to dryness. The neutral residue (80 mg) was recrystallized from chloroform–benzene to give the γ-lactone VIII, m.p. 210–214°. (Found: C, 64·64; H, 6·68; O, 29·06. $C_{21}H_{26}O_7$ requires: C, 64·59; H, 6·71; O, 28·70%).

Oxidation of desoxodicarboxylic acid monoester (X; R = CH_3) *with lead tetraacetate.* The oily monoester (780 mg), prepared by methylation of desoxodicarboxylic acid X (R = H),[44] m.p. 275–280°, with methanolic HCl, was reacted with 1·1 g of $Pb(OAc)_4$ in boiling dry benzene (100 ml) for 15 hr. The solvent was evaporated, the residue suspended in chloroform and the suspension was extracted repeatedly with aqueous $NaHCO_3$. Evaporation of $CHCl_3$ gave a neutral fraction (580 mg) which was hydrolyzed with boiling methanolic NaOH (1%) for 30 min. A conventional separation gave an acidic fraction (350 mg), which was subjected to a chromatography on silicic acid (silica gel, Light and Co). Fractions eluted with benzene–ether (1:1) (170 mg) were distributed in 9 funnels between $CHCl_3$ and a phosphate–citrate buffer (pH 7) (50 ml in each phase). The peak fraction (105 mg) was esterified with diazomethane and crystallized from ether to give the unsaturated ketone XI, m.p. 102–106°. (Found: C, 69·42; H, 8·48; O, 22·32; OCH_3, 16·90. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34; O, 22·08; 2 OCH_3, 17·1%.)

Oxidation of anhydroneoquassin with $KMnO_4$. Anhydro*neo*quassin, m.p. 196°, was prepared according to the method of Clark[a] and Robertson[b]. To the stirred solution of anhydro*neo*quassin (2·0 g) in pure acetone (250 ml) and dist. H_2O (100 ml), a solution of $KMnO_4$ (2·06 g) in dist. H_2O (100 ml) was added dropwise at room temperature over a period of about 15 min. After filtration of the reaction mixture through Celite and washing of the cake with acetone, the combined filtrate was partially evaporated *in vacuo*. Epoxide XXII, which separated during the evaporation, was filtered (240 mg) and recrystallized from ethyl acetate–chloroform, m.p. 222–224°. (Found: C, 65·07; H, 6·94; O, 27·52. $C_{22}H_{28}O_7$ requires: C, 65·34; H, 6·98; O, 27·68%.)

The mother liquor was made strongly basic by the addition of 10% KOH(10 ml) and exhaustively extracted with chloroform. Evaporation of the combined extracts left a white foam (520 mg) which was crystallized from a minimum amount of ethyl acetate. Two subsequent recrystallizations from methanol–isopropyl ether yielded pure XVI, m.p. 213°. (Found: C, 64·90; H, 7·48; O, 27·28. $C_{22}H_{30}O_7$ requires: C, 65·01; H, 7·44; O, 27·55%), I.R.$_{max}$ 3400, 1705 (infl.), 1685 and 1637 cm^{-1}; U.V.$_{max}$ 258 mμ, ε 12,000.

Extraction of the acidified (HCl) aqueous solution with chloroform and evaporation of the solvent yielded a foam which on treatment with ethyl acetate deposited crystals of XV, recrystallized from methanol, m.p. 254–260° (dec.). (Found: C, 65·28; H, 6·98; O, 27·83. $C_{22}H_{28}O_7$ requires: C, 65·34; H, 6·98; O, 27·68%.)

Oxidation of XVI *with* H_5IO_6. A mixture of XVI (300 mg), pure acetone (50 ml), H_5IO_6 (115 mg) and H_2O (5 ml) was stirred overnight at room temperature. After partial evaporation of acetone and dilution of the reaction mixture with dist. H_2O, the reaction products were extracted with chloroform. The foamy product obtained after evaporation of the solvent was kept for 30 min in aqueous methanolic KOH. The solution was diluted with H_2O, extracted with $CHCl_3$, the solvent removed *in vacuo* and the resulting oil (160 mg) refluxed overnight in 70% ethanol in the presence of freshly prepared Ag_2O (from 1·0 g $AgNO_3$). After filtration through Celite, the reaction mixture was evaporated to a small volume, diluted with H_2O, made alkaline with NaOH (100 mg) and extracted with $CHCl_3$. Evaporation of the solvent yielded a neutral fraction (89 mg) which was dissolved in pyridine (20 ml). CrO_3 (90 mg) in pyridine (20 ml) was then added and the mixture left standing overnight. Evaporation of the reaction mixture *in vacuo* and extraction of the residue with $CHCl_3$, followed by decoloration of the solution with charcoal and removal of the solvent, yielded the γ-lactone which was crystallized from methanol and then from methanol–isopropyl ether, m.p. 266–268°. (Found: C, 67·13; H, 6·77; O, 26·15. $C_{21}H_{26}O_6$ requires: C, 67·36; H, 7·00; O, 25·64%.)

Acidification of the aqueous layer from the Ag_2O oxidation followed by extraction with $CHCl_3$ yielded crystalline XV (identical m.p., I.R.).

Treatment of XV *with aqueous* KOH. A solution of XV (70 mg) in 5% aqueous KOH (20 ml) was left standing for 3 days at room temperature. Neutral material was extracted with $CHCl_3$, the solvent removed *in vacuo*, the residue redissolved in aqueous methanolic KOH (1:1, 5%, 20 ml) and refluxed for 3 hr. After dilution with H_2O, the reaction product was extracted with $CHCl_3$. Removal of the solvent *in vacuo* gave an oily residue (38 mg), which was crystallized from ethyl acetate–isopropyl ether. Pure XVIII decomposed at 183–208°. (Found: C, 68·94; H, 8·06; O, 23·05. $C_{20}H_{32}O_5$ requires: C, 68·94; H, 8·10; O, 22·96%), I.R.$_{max}$ (KBr) 3450, 1695, 1675, 1650 and 1635 cm^{-1}.

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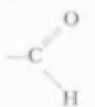
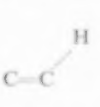
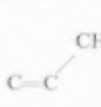
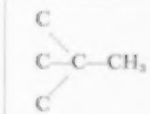
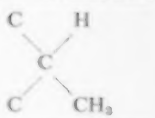
TABLE 1.—IMPORTANT NMR SIGNALS OF QUASSIN AND ITS DERIVATIVES*

Compound				OCH_3			
Quassin		4·71*d* (2)	5·70*t*	6·38 6·44	8·15	8·45 8·79	8·86*d* (5·6)
*Neo*quassin		4·75*d* (2)	5·26*t* 6·15*m*	6·38 6·41	8·15	8·46 8·94	8·89*d* (5·6)
Deuterated *neo*quassin		4·72*d* (2)	5·26*m*; 0·5H 6·15*m*	6·36 6·45		8·45 8·89	8·85*t* (5·4)
Dihydro*neo*quassin			4·61*t* 5·52*m* 6·10*m*	6·40 6·59	8·16	8·50 8·95*d* (1·1)	9·10*d* (5·6)
Deuterated dihydro*neo*quassin			5·20*m*; 0·5H 6·07*m*	6·36 6·56		8·58 8·94 (1·1)	9·10*d* (5·6)
Norketone (XI)			6·3*m*	6·35; 6H	7·95 8·16	8·94	9·21*d* (6·3)
Anhydro*neo*quassin		3·67*m* 4·77*d* (2) 5·48*m*	6·25*m*	6·40 6·46	8·13	8·58 8·88	8·90*d* (5·4)
Dehydro*neo*quassin (XX)		4·43*d* (4·5)	4·22*d* (4·5)	6·27	8·05	8·48	8·84*d* (5·6)
Dehydroquassin (XXI)		4·72*d* (2) 3·97 4·61*d* (2)	6·05*m* 5·72*m*	6·44 6·22 6·41	7·98	8·89 8·48 8·75	8·90*d* (5·6)
Phenol (XXIV)	—0·44 0·60*m*	5·19*d* (2)		6·27	7·46 7·53	8·59	9·00*d* (5·6)

* The spectra were determined in $CDCl_3$ with a Varian instrument at 56·4 Mc/sec. The values are given in p.p.m. relative to $(CH_3)_4Si$ as an internal reference. Unless specified, all signals in the first three columns correspond to 1 H, all those in the last four columns to 3 H atoms. Singlets are unmarked, while multiplets are described by the following abbreviations: *d*, doublet; *t*, triplet; *m*, incompletely resolved multiplet. Numbers in brackets denote splitting constants in cycles/sec.

An isomeric product showing I.R. bands (in KBr) at 3450, 1690, 1660 and 1630 cm^{-1}, m.p. 184–221° (dec.), was obtained when XV was treated with 5% aqueous KOH for 4 hr under reflux. (Found: C, 69·00; H, 8·06; O, 22·88. $C_{20}H_{28}O_5$ requires: C, 68·94; H, 8·10; O, 22·96%.)

The two compounds are probably epimers.

Dehydroneoquassin (XX). The compound was obtained from the mother liquors of anhydro*neo*-quassin by evaporation to dryness and crystallization of the residue from CH_3OH. In contrast to Clark's results,[3] the pure product, m.p. 194–196°, crystallized as a monohydrate. (Found: C, 65·26; H, 7·17; O, 27·41. $C_{22}H_{28}O_6 \cdot H_2O$ requires: C, 65·02; H, 7·43; O, 27·55%.)

Oxidation of XX *with* Ag_2O. A mixture of XX (0·5 g), 70% ethanol (75 ml) and freshly prepared Ag_2O (from 2 g of $AgNO_3$) was refluxed overnight. After filtration through Celite, partial evaporation of the alcohol and dilution with H_2O, unchanged XX was removed from the basified solution (10% NaOH, 5 ml) by extraction with $CHCl_3$. The reaction product was then extracted from the acidified aqueous solution with $CHCl_3$. Removal of the solvent *in vacuo* left a foam which was crystallized from ethyl acetate. Crystalline XXI decomposed at 210–221°C even after repeated recrystallization from CH_3OH. (Found: C, 68·72; H, 7·07; O, 24·78. $C_{22}H_{24}O_6$ requires: C, 68·38; H, 6·78; O, 24·84%.)

Demethylation of XXII *with* HCOOH *in acetone*. A mixture of XXII (100 mg), pure acetone (50 ml) and 90% HCOOH (1·2 ml) was left standing at room temperature for 48 hr. After partial evaporation of acetone *in vacuo* and dilution of the reaction mixture with H_2O, the reaction product was extracted with $CHCl_3$. Yellow foam (100 mg) obtained after solvent evaporation was crystallized from ethyl acetate–chloroform to give pure XXIII, m.p. 230–234° (dec.). (Found: C, 64·60; H, 6·65; O, 28·86; OCH_3, 7·95. $C_{21}H_{26}O_7$ requires: C, 64·61; H, 6·71; O, 28·68; 1 OCH_3, 7·95%.)

Treatment of XXIII *with* KOH. Treatment of XXIII with aqueous methanolic KOH for 30 min at room temperature converted it to phenol XXIV, which was extracted from the diluted and acidified solution with chloroform. Two recrystallizations from ethyl acetate gave pure XXIV, m.p. 229–230°. (Found for a dried sample: C, 66·03; H, 6·52; O, 27·34; OCH_3, 8·74; for a sublimed sample: C, 66·69; H, 6·92; O, 26·16. $C_{20}H_{24}O_6$ requires: C, 66·65; H, 6·61; O, 26·92; 1 OCH_3, 8·61%.)

The identical product (U.V., I.R., m.p.) was obtained when a mixture of XXII (100 mg), CH_3OH (50 ml), H_5IO_6 (113 mg), $NaHCO_3$ (100 mg) and H_2O (20 ml) was stirred at room temperature overnight, then concentrated *in vacuo* and the separated crystalline intermediate treated with aqueous methanolic KOH. XXIV was then extracted from the reaction mixture with chloroform.

Acknowledgements—The deuteration experiments were performed by Mr. A. H. Gray. We thank Dr. R. Thomas, The Squibb Institute for Medical Research, New Brunswick, N.J., for a private communication in which he independently considered the oxidative coupling biogenesis for quassin and the possible attachment of one methyl group at C_9.

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CHEMICAL INVESTIGATION OF *CITRUS MITIS* BLANCO—III

ISOLATION OF TWO NEW FLAVANONES

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Abstract—From the peels of *Citrus mitis* Blanco., two new flavanones, Citromitin (5,6,7,8,3′,4′-hexamethoxyflavanone) and 5-O-desmethylcitromitin (5-hydroxy-6,7,8,3′,4′-pentamethoxyflavanone) were isolated by extraction with petroleum ether.

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THE ripe fruit of *Citrus mitis* Blanco.[1,2] is reddish orange in colour and the size of a lemon. The weight of a fruit varies from 25–30 g and the juice and peels form 20–25 per cent and 30–37 per cent respectively of the weight of the fruit.

The similarity of *C. mitis* Blanco. to kamala (*Citrus aurantium*) and the lack of chemical information prompted the investigation. The petroleum ether extract of the peels furnished a bright yellow crystalline solid which could be separated into a neutral compound (A), a phenolic compound (B) and a third crystalline compound (C) identification of which could not be achieved on account of poor yield.

Citromitin ($C_{21}H_{24}O_8$, $\frac{1}{2}H_2O$; m.p. 134–136°) was considered to be a flavanone as it developed a deep red violet colour with sodium borohydride and concentrated hydrochloric acid.[3] Functional group analysis indicated six methoxyls in the molecule. As no hexamethoxyflavanone is known to occur in nature, compound A was considered to be a new flavanone and hence named Citromitin.

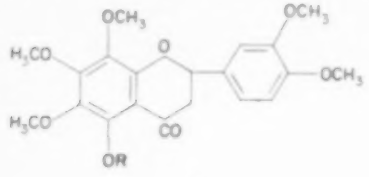
Citromitin could be readily converted into the corresponding chalkone ($C_{21}H_{24}O_8$, 1-H_2O; m.p. 116–117°) which on oxidation with pyridine and iodine or with alkaline hydrogen peroxide furnished veratric acid. During prolonged alkaline hydrolysis of citromitin, the chalkone was formed as the major product (68 per cent) along with a minor quantity of veratric acid (17 per cent). The chalkone character of the hydrolytic product was further established by its reconversion into citromitin by refluxing with 3 per cent alcoholic sulphuric acid. These facts suggest that citromitin is a flavanone with a 3′,4′-dimethoxyphenylside nucleus. If out of the six methoxyls two are thus fixed, the remaining four must be present in the benzopyrone structure presumably in 5, 6, 7, 8, positions. Citromitin may, therefore, be represented as 5,6,7,8,3′,4′-hexamethoxyflavanone (I, R = CH_3) and the chalkone as 2-hydroxy-3,4,5,6,3′,4′-hexamethoxychalkone (II).

A hexamethoxyflavanone of this constitution (I, R = CH_3) and the corresponding chalkone (II) were synthesized earlier by Oliverio and Casinovi[4] who reported melting points (119° and 97–98°) much lower than that of citromitin and its chalkone. For comparison with an authentic specimen the synthesis was repeated and the synthetic 2-hydroxy-3,4,5,6,3′,4′-hexamethoxychalkone (II, m.p. 112–114°) was identical with

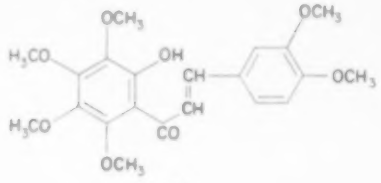
[1] G. P. Sastry and L. R. Row, *J. Sci. Ind. Res.* **19B**, 500 (1960).
[2] G. P. Sastry and L. R. Row, *J. Sci. Ind. Res.* **20B**, 187 (1961).
[3] Robert M. Horowitz, *J. Org. Chem.* **22**, 1733 (1957).
[4] A. Oliverio and C. Casinovi, *Chem. Abstr.* **46**, 978b (1952).

the chalkone from citromitin. It was cyclized as before and the resulting flavanone (I, R = CH_3; m.p. 132–134°) was identical with natural citromitin.

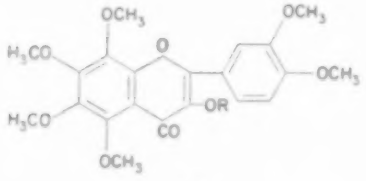
Citromitin is the first completely methylated flavanone to be isolated from the citrus fruits and forms the second known flavanone with 5, 6, 7, 8, substitution, the first being isopedicin[5] (6-hydroxy-5,7,8,-trimethoxyflavanone) occurring in the leaves of *Didymocarpus pedicellata* R.Br. (*Gesneraceae*) along with its chalkone, pedicin.



I



II



III

It may be of interest to mention that the completely methylated chalkone, pedicellin, also occurs in the leaves of the same plant. Closely related flavones, nobiletin,[6] (5,6,7,8,3′,4′-hexamethoxyflavone), 5-O-desmethylnobiletin[7] as well as the lower member, ponkanetin,[8] (5,6,7,8,4′-pentamethoxyflavone), have been isolated from the citrus fruits.

The flavanone character of citromitin was further proved by converting it into the corresponding 3-hydroxyflavone (III, R = H) by the modified Kostanecki's synthesis of Row and Seshadri.[9] The 3-hydroxy-hexamethoxyflavone thus obtained gave rise to a heptamethoxyflavone (III, R = CH_3) m.p. 129–130°, agreeing with that already recorded in literature.[10] Selenium dioxide oxidation[8] of citromitin furnished nobiletin in good yield.

Compound B ($C_{20}H_{22}O_8$, m.p. 146–147°) is also a flavanone as it exhibits reddish pink colour with sodium borohydride and hydrochloric acid.[3] Analysis indicated five methoxyls in the molecule and complete methylation yielded a hexamethoxyflavanone identical with citromitin. From the ferric chloride colouration (greenish brown), compound B may be regarded as 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavanone (I, R = H) and hence named 5-O-desmethylcitromitin. This constitution (I, R = H) for compound B was shown to be correct by its synthesis from citromitin. The latter was demethylated with hydriodic acid to give hexahydroxyflavanone which could be remethylated back to citromitin. The formation of a stable hexahydroxyflavanone during demethylation suggests that the stability could have been

[5] K. V. Rao and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **27A**, 375 (1948).
[6] K. F. Tseng, *J. Chem. Soc.* 1003 (1938).
[7] P. S. Sarin and T. R. Seshadri, *Tetrahedron* **8**, 64, (1960).
[8] J. M. Sehgal, T. R. Seshadri and K. L. Vadhera, *Proc. Ind. Acad. Sci.* **42A**, 252 (1955).
[9] L. R. Row and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **21A**, 248 (1945).
[10] V. Venkateswarlu and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **23A**, 354 (1946).

caused by chelation between the 5-hydroxyl and the carbonyl group.[11] Methylation of the hexahydroxyflavanone with excess diazomethane gave rise to a 5-hydroxypentamethoxyflavanone (I, R = H) melting at 146–147°, alone or mixed with compound B.

EXPERIMENTAL

The sun-dried peels (4 kg) of *C. mitis* Blanco were powdered in a disintegrator and exhausted successively with pet ether (b.p. 40–60°), ether and methanol in a large soxhlet extractor.

Examination of petroleum ether extract. Upon concentration, the extract deposited a yellow crystalline solid in an hour. After 48 hr, the solid was collected at the pump and shaken with 3% aqueous alcoholic (1:1) sodium hydroxide. The alkaline layer was repeatedly extracted with ether and the total ether extract (800 ml) evaporated to get the neutral compound (A); yield: 8·2 g. The alkaline layer was acidified and extracted with ether. Evaporation of the ether deposited a phenolic compound (B); yield: 1·1 g.

The mother liquor was steam distilled to collect the orange peel oil. The residue was extracted several times with pet ether (10 × 100 ml), the extract washed with conc HCl (5 × 25 ml) and the washings dropped into ice-cold water. The separated solid is designated compound C; yield: 150 mg.

Examination of compound A

Citromitin. Compound A was crystallized thrice from methanol and finally from benzene–pet ether (1:4) as fine lemon yellow needles m.p. at 134–136°. (Found: C, 61·19: H, 5·95; OCH_3, 45·33; $C_{21}H_{24}O_8$–$\frac{1}{2}H_2O$ requires: C, 61·01; H, 6·05; 6-OCH_3, 45·03%). U.V. Spectrum in 95% ethanol[12] has λ_{max} 335, 272 (inflexion) and 250 mμ (log ε, 4·38, 4·23, and 4·32). It gave no colour with alcoholic $FeCl_3$, and a bright reddish violet colour with sodium borohydride and HCl and also with Mg–HCl.

Alkaline hydrolysis of citromitin. A solution of citromitin (2 g) in 8% absolute alcoholic potassium hydroxide (60 ml) was refluxed for an hour on a water bath. Alcohol was removed under red press and HCl added. The resulting bright yellow crystalline solid separated from methanol after two crystallizations as bright orange flakes; m.p. 116–117°; yield: 1·65 g (Found: C, 59·99; H, 5·90; OCH_3, 44·29; $C_{21}H_{24}O_8$–$1H_2O$ requires: C, 59·71; H, 6·16; 6-OCH_3, 44·08%). U.V. Spectrum in 95% ethanol has peaks at λ_{max} 382 and 288 mμ (log ε, 4·30 and 4·09). It developed a brown colour with alcoholic $FeCl_3$ and with sodium borohydride–HCl only a yellow colour.

When the hydrolysis of citromitin was repeated refluxing the liquid for 8 hr, a small quantity of veratric acid (17%) was obtained along with the chalkone (68%).

Conversion of the chalkone into citromitin. A solution of the above chalkone (500 mg) in 3% alcoholic sulphuric acid (50 ml) was refluxed for 30 hr. Removal of the solvent under red press followed by addition of water deposited a pale yellow solid which crystallized from methanol as lemon yellow needles, m.p. 134–136°, undepressed by citromitin. Yield: 450 mg.

Synthesis of 2-hydroxy-3,4,5,6,3′,4′,-hexamethoxychalkone

To a solution of 2-hydroxy-3,4,5,6,-tetramethoxyacetophenone[13] (200 mg) and veratrie aldehyde (1·3 g) in ethanol (10 ml) was added aqueous sodium hydroxide (3 g in 3 ml) in small quantities while cooling in ice. The flask was corked airtight and kept at room temp for 2 days. The deep red viscous liquid was worked up as usual. The chalkone crystallized from methanol as orange yellow crystalline plates, m.p. 112–114°, unchanged by the chalkone from citromitin. Yield; 85 mg. (Found: C, 59·85; H, 5·98%).

The chalkone (45 mg) was refluxed with 3% alcoholic sulphuric acid (10 ml) for several hours; the product was a pale yellow crystalline solid, m.p. 130–133° undepressed by admixture with citromitin.

Demethylation of citromitin: 5,6,7,8,3′,4′-hexahydroxyflavanone

Hydriodic acid (50 ml *d.* 1·7) was added to a solution of citromitin (1 g) in acetic anhydride (10 ml) and refluxed for 3 hr, cooled and diluted with a solution of sodium bisulphite. The hexahydroxyflavanone was filtered and crystallized from aqueous acetic acid in the form of yellow crystalline solid

[11] N. N. Chari and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **27A**, 223 (1940).
[12] The U.V. measurements reported in this paper were made on Hilgers Uvispek photoelectric colorimeter.
[13] W. Baker, *J. Chem. Soc.* 666 (1941).

which did not melt below 340°; yield 540 mg. (Found: C, 52·05; H, 4·33; $C_{15}H_{12}O_8$–$1\frac{1}{2}H_2O$ requires: C, 51·88; H, 4·32%). It developed greenish brown colour with alcoholic $FeCl_3$, bright red with Mg–HCl and orange red with sodium borohydride and HCl. It changed yellow to greenish brown in 5% sodium bicarbonate, yellow to brownish yellow in 5% sodium hydroxide (10 sec) and red to deep crimson red in 5% sodium carbonate (40 sec).

The hexaacetyl derivative (Ac_2O and Na Ac) crystallized from methanol as colourless needles, m.p. 225–227°. (Found: C, 57·02, H, 4·51; $C_{27}H_{24}O_{14}$ requires: C, 56·63; H, 4·20%).

Methylation of 5,6,7,8,3′,4′-hexahydroxyflavanone

(a) *Synthesis of 5-O-desmethylcitromitin.* An ethereal solution of diazomethane was added in excess to an alcoholic solution of the hexahydroxyflavanone (500 mg). After 36 hr at 0°, the solvent was evaporated and the residue crystallized from methanol as light yellow rhombic plates, m.p. 146–147°, undepressed by compound B, yield: 450 mg. (Found: C, 61·64; H, 5·82; OCH_3, 39·16; $C_{20}H_{22}O_9$ requires: C, 61·51; H, 5·60; 5-OCH_3, 39·74%). It exhibited a brown colour with alcoholic $FeCl_3$.

(b) *Remethylation to citromitin.* The hexahydroxyflavanone (200 mg) was refluxed for 12 hr with anhydrous potassium carbonate (3 g) and dimethyl sulphate (0·9 g) in acetone solution. The methyl ether was separated as usual and crystallized from benzene–pet ether (1:4) as lemon yellow needles, m.p. 134–136° unchanged by citromitin, yield: 150 mg.

Synthesis of 3-hydroxy-5,6,7,8,3′,4′-hexamethoxyflavone

To a gently boiling solution of citromitin (500 mg) in alcohol (50 ml), freshly distilled amyl nitrite (3·5 ml) and conc HCl (*d* 1·19; 35 ml) were added alternately in small quantities with stirring. The solution turned bright yellow at first and finally bright reddish orange. The hot solution was cooled and diluted. It was extracted with ether several times and the ether extract shaken with 3% alkali. On acidification of the alkaline layer an yellow solid was obtained which crystallized from alcohol in the form of prismatic rods, m.p. 141–143°, yield 100 mg. (Found: C, 60·43; H, 5·51; OCH_3, 45·12: $C_{21}H_{22}O_9$ requires: C, 60·29; H, 5·26; 6-OCH_3, 44·49%). It developed brown colour with alcoholic $FeCl_3$.

3,5,6,7,8,3′,4′-Heptamethoxyflavone. The above 3-hydroxyflavone (100 mg) was refluxed for 4 hr in acetone (30 ml) with potassium carbonate (1 g) and dimethyl sulphate (0·6 ml). The methyl ether crystallized from alcohol as colourless needles, m.p. 128–129°; yield: 80 mg. (Found: C, 61·19; H, 5·99: $C_{22}H_{24}O_9$ requires C, 61·10; H, 5·56%). No colour was developed with alcoholic $FeCl_3$; but only a pale yellow colour with sodium borohydride and HCl.

Selenium dioxide oxidation of citromitin. Citromitin (340 mg) in isoamyl alcohol (8 ml) was refluxed with selenium dioxide (340 mg) for 12 hr at 140–145°. Metallic selenium was filtered off and the filtrate steam distilled to remove the amyl alcohol. The residue crystallized from methanol as colourless needles, m.p. 134–136°; mixed m.p. with citromitin 82–117°. It did not answer the colour test with sodium borohydride and HCl for flavanone. Tseng[4] records m.p. 134° for nobiletin. (Found: C, 62·42; H, 5·63; $C_{21}H_{22}O_9$ requires: C, 62·69; H, 5·47%).

Examination of compound B

5-O-*Desmethylcitromitin.* Compound B crystallized from methanol as light yellow rhombic plates, m.p. 146–147° undepressed by synthetic 5-O-desmethylcitromitin (see above). (Found: C, 61·82; H, 5·92; OCH_3, 40·05; $C_{20}H_{22}O_9$ requires: C, 61·51; H, 5·60; 5-OCH_3, 39·74%). U.V. Spectrum in 95% ethanol has λ_{max} 344 and 283 and 255 mμ (log ε, 4·37, 4·28 and 4·19). It gave dark brown colour with alcoholic $FeCl_3$, bright violet colour with Mg–HCl and reddish pink colour with sodium borohydride and HCl.

Methylation of 5-O-desmethylcitromitin. Compound B (200 mg) was methylated in anhydrous acetone (80 ml) with anhydrous potassium carbonate (2 g) and dimethyl sulphate (1 ml). The methyl ether crystallized from methanol; m.p. 134–135° alone or mixed with citromitin.

Examination of compound C

Compound C was crystallized from alcohol as light yellow needles, m.p. 141–143°. (Found: C, 61·93; H, 5·07; $C_{20}H_{20}O_8$ requires: C, 61·80; H, 5·15%). It developed brown colour with alcoholic $FeCl_3$, only a yellow colour with sodium borohydride and HCl and a bright reddish violet colour with Mg–HCl.

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SYSTEMATIK UND NOMENKLATUR DER LIGNANE

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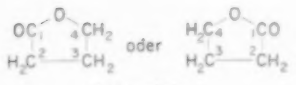
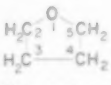
Abstract—A system of notation for the lignans and isolignans is proposed. The name cyclolignans instead of isolignans has been suggested. The notation is based on the oxygen equivalents in the benzene rings and side chains. The basic hydrocarbons are designated as lignan and cyclolignan.

UNTER Lignanen werden Phenole verstanden, deren Formel zwei C_6C_3-(Phenylpropan) Einheiten aufweist, die am mittelständigen Kohlenstoffatom der Seitenkette verknüpft sind. Ohne Zweifel entstehen sie in der Natur auf diese Weise; für einige ist dies bewiesen. Sie treten in zwei Typen auf: dem eigentlichen Lignan I und dem sogenannten Isolignan II, das wir Cyclolignan nennen. Denn es ist kein Isomeres des ersteren; es besitzt zwei Wasserstoffatome weniger und enthält das Ringsystem des Tetrahydro-naphthalins.

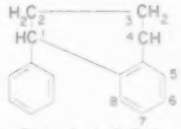
Die strenge systematische Nomenklatur dieser Substanzen ist unübersichtlich, denn sie stützt sich auf Butan, Butyrolakton oder Butanolid—(4,1), Tetrahydrofuran, Tetrahydro-naphthalin und Dioxa-bicyclo-octan.[1] Die gebräuchlichen Bezifferungen lauten:



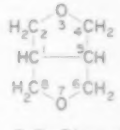
Butanolid



Tetrahydro-furan



1-Phenyl-1.2.3.4-tetrahydro-naph-thalin

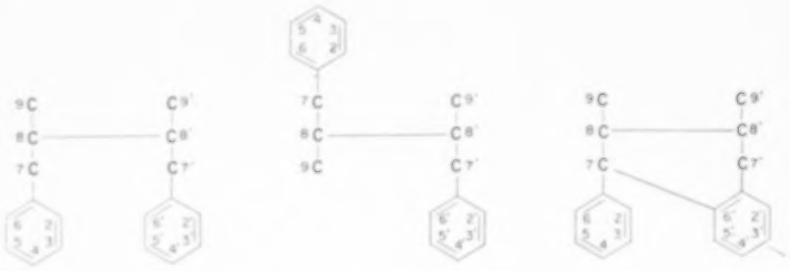


3.7-Dioxo-bi-cyclo-[3.3.0]-octan

Welche der beiden Schreibweisen des Butanolids angewendet wird, richtet sich nach den zugehörigen Cyclolignanen (z.B. 33 Hydroxymatairesinol und 35 Conidendrin). Cyclische Äther haben neuerdings international und im "Beilstein" das Präfix "epoxy" (statt oxido) erhalten, auch wenn die Zahl der Ringglieder höher als 3 ist. Tetrahydrofuran ist demnach 1·4-Epoxy-butan. Die alte Nomenklatur soll nicht angetastet werden. Dasselbe gilt für die Benennung der asymmetrischen Formen nach Cahn *et al.*[2] Neuere Übersichten über die Lignane stammen von Hearon und MacGregor[3] sowie von Erdtman[4] und Karrer.[5]

[1] Herrn F. Richter, Beilstein-Institut, danken wir für die Durchsicht des Manuskripts.
[2] R. S. Cahn, C. K. Ingold u. V. Prelog, *Experientia* **12**, 81 (1956).
[3] W. M. Hearon u. W. S. MacGregor, *Chem. Rev.* **55**, 957 (1955). Im Text zitiert: Hearon.
[4] H. Erdtman in *Moderne Methoden der Pflanzenanalyse* (Herausgegeben von K. Paesch und M. V. Tracey) Band III., p. 428. Springer Verlag, Berlin (1955). Zitiert: Erdtman.
[5] W. Karrer, *Konstitution und Vorkommen der org. Pflanzenstoffe*. Birkhäuser Verlag, Basel u. Stuttgart (1958). Zitiert: Karrer mit der von W. Karrer verwendeten Numerierung.

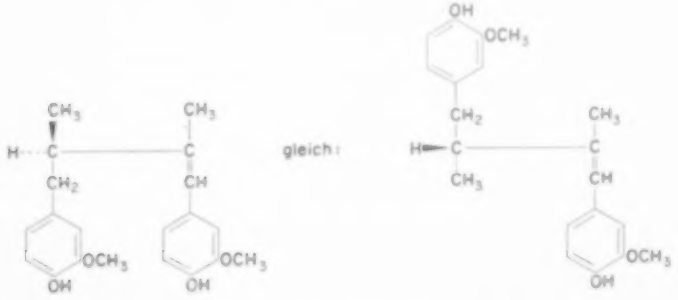
Im folgenden wird versucht, eine leicht verständliche Systematik und Nomenklatur aus den beiden Typen abzuleiten, für welche die Bezeichnungen Lignan (I) und Cyclolignan (II) vorgeschlagen werden:



I Lignan I a Lignan II Cyclolignan

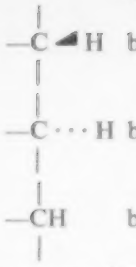
Die beiden aus C_6C_3-Einheiten bestehenden Molekülhälften werden senkrecht nebeneinander geschrieben. Wenn bei einem Lignan (I) wegen Äther- oder Lactonbindungen eine Molekülhälfte um die Achse 8–8′ gedreht werden muss, so wird hierzu die linke verwendet (Ia). Die Cyclolignane (II) werden immer so geschrieben, dass die Molekülhälfte, deren Benzolkern am Tetrahydronaphthalin-system teilnimmt, rechts steht. Auf diese Weise kann die übliche Nummerierung in den Benzolkernen eingehalten werden. Die Bezifferung geht von der üblichen Kennzeichnung der Benzolkohlenstoffatome aus. In der rechten Molekülhälfte wiederholt sich die Bezifferung mit hochgesetzten Strichen. Bei der Bezifferung eines Lactons (-olids) hat die Carbinolgruppe den Vorrang.

Die Raumformeln stützen sich auf die Feststellung der absoluten Konfiguration der Guajakharzsäure III und IIIa von Schrecker und Hartwell[6] sowie Carnmalm.[7]



Zur Kennzeichnung sterischer Unterschiede werden die asymmetrischen Kohlenstoffatome, deren Wasserstoffatom oder tertiäres Hydroxyl bei der Schreibweise I (Ia) oder II aus der Papierebene nach oben herausragt, mit α bezeichnet, im anderen Fall mit β.

[6] A. W. Schrecker u. J. L. Hartwell, *J. Org. Chem.* **21**, 381 (1956); *J. Amer. Chem. Soc.* **79**, 3827 (1957).
[7] B. Carnmalm, *Chem. & Ind.* 1093 (1956); *Ark. Kemi* **15**, 215 (1960).



—C◢H bedeutet H über der Ebene (α-Stellung)

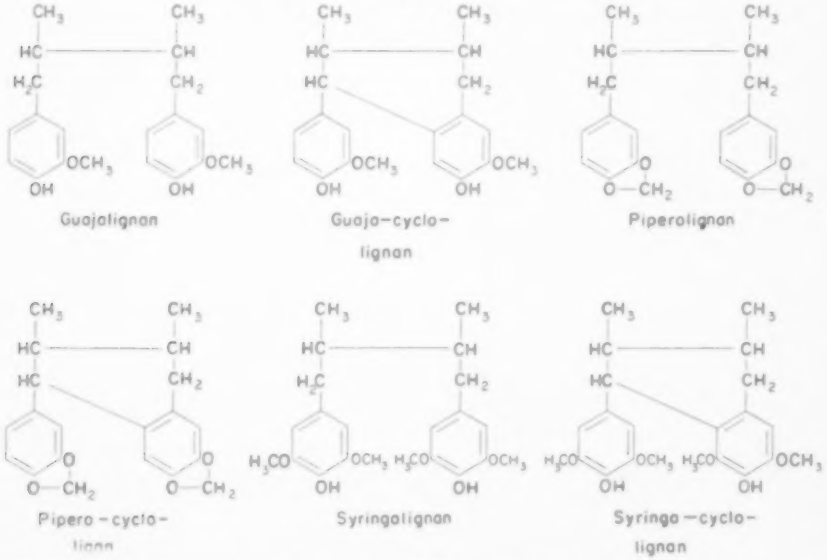
—C···H bedeutet H unter der Ebene (β-Stellung)

—CH bedeutet keine Angabe der Lage des H-Atoms.

Steht ein asymmetrisches C-Atom in einer offenen Kette, so wird das Oben- *und* Unten-Zeichen (◢ und ···) angebracht (z.B. voranstehende Formel). Steht es in einem (eben gedachten) Ring, so genügt eines dieser Zeichen.

Wenn in Lignanen Äthergruppen in der Formel zur Drehung einer Molekülhälfte um die 8-8′-Achse zwingen, so wird—wie schon erwähnt—bei der Niederschrift die linke Hälfte gedreht. Dabei erhalten die Wasserstoffatome der linken Hälfte, die vorher die α-Lage innehatten, die β-Lage und umgekehrt. Dies ergibt sich auch aus der Regel, dass nur bei *doppeltem* Umtausch die Konfiguration erhalten bleibt. Wenn z.B. in III die linke Molekülhälfte durch Auswechslung der Benzyl- und Methylgruppen herumgedreht wird, so muss man, um die Konfiguration wiederherzustellen, das H-Atom über die Ebene legen (IIIa). Die Bezeichnung α und β gibt somit nur die Lage des H-Atoms bei der gerade vorliegenden Schreibweise an; daraus kann die Konfiguration abgeleitet werden. Aus dem Zusammenhang geht von selbst hervor, wann die parallele Schreibweise I oder die antiparallele Ia verwendet wird (bei Lignanen mit Ätherbrücken von 7 nach 9′ und (oder) 9 nach 7′).

Diese Nomenklatur hat den Vorteil, dass die Zugehörigkeit zu den Lignanen und Cyclolignanen aus dem Namen der Substanz hervorgeht und die stereochemische Anordnung einfach ausgedrückt werden kann. Eine weitere Vereinfachung ist möglich, wenn die beiden Benzolkerne gleich substituiert sind:



Alle übrigen Substituenten werden in der üblichen Weise bezeichnet.

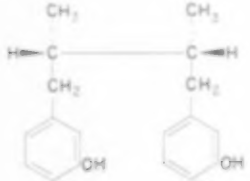
Die Einteilung folgt der Zahl der Sauerstoffatome im linken, danach im rechten Benzol ring; hierdurch werden die durch zwei Ziffern ausgedrückten Klassen gebildet (z.B. 2:2 für die ersten 39 Substanzen; 3:2 für die Substanzen 41–46 u.s.w.).

Innerhalb der Klassen richtet sich die Reihenfolge nach der Oxydationsstufe ausserhalb der Benzolkerne; Hydroxylsauerstoff zählt einmal, Carbonyl und Äther zweimal, Carboxyl dreimal, Lacton viermal. Eine Äthylenbindung zählt wie ein Hydroxyl, ebenso die Cyclisierung zum Cyclolignan. Der Klassenbezifferung wird hierfür eine römische Ziffer angehängt. Fehlen ausserhalb der Benzolkerne Sauerstoffäquivalente, so wird anstelle einer römischen Ziffer O gesetzt. Cyclolignane rangieren zwischen den Lignanen, denen sie zugehören. Ein Beispiel möge dies erläutern. Hydroxy-matairesinol 34 besitzt an C7 und 9 je ein Sauerstoffäquivalent, an C9′ drei Äquivalente, zusammen V; das Conidendrin 38 erhält mit 4 Sauerstoffäquivalenten und einer Cyclisierung dieselbe Ziffer.

In der folgenden Übersicht sind die uns zugänglichen Formeln von natürlichen Lignanen angeführt; dabei sind angegeben: in der Überschrift die Nummer, die Bezifferung und der übliche Gebrauchsname, unter (a) die aus Beilsteins Handbuch entnommene oder nachgebildete systematische Bezeichnung, unter (b) die vorgeschlagene neue Bezeichnung unter Einschluss der Konfiguration (α oder β), unter (c) die verkürzte Bezeichnung mit der systematischen Konfigurationsangabe (R oder S).[2] Die Bezeichnung (c) fällt weg, wenn sie gegenüber (b) keine Vereinfachung bedeutet.

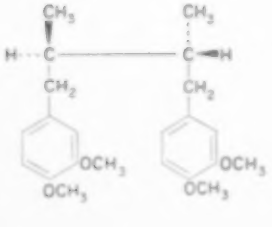
3 Kunstprodukte (2, 32, 45) sind wegen ihres Zusammenhanges mit den Naturstoffen mit aufgezählt.

In verschiedenen Fällen konnten mit Hilfe des Drehungsvermögens oder sterischer Überlegungen neue konfigurative Zuordnungen abgeleitet werden (6, 7, 14, 15, 33, 48, 49).



(1) 2:2:0 *Nor-dihydro-guajakharzsäure optisch inaktiv; Mesoform*

(a) 2.3-Dimethyl-1.4-bis-[3.4-dihydroxy-phenyl]-butan
(b) 3.4.3′.4′-Tetrahydroxy-α8.α8′ oder β8.β8′-lignan
Hearon 964; Erdtman 432; Karrer 1167

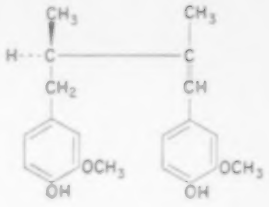


(2) 2:2:0 *(—)-Dihydro-guajakharzsäure-dimethyläther*

(Kunstprodukt, entstanden durch Hydrierung von (—)-Guajakharzsäure-dimethyläther neben Mesoform.)
(a) 2.3-Dimethyl-1.4-bis-[3.4-dimethoxy-phenyl]-butan
(b) 3.4.3′.4′-Tetramethoxy-β8.α8′-lignan
(c) (8R8′R)-Guajalignan-dimethyläther

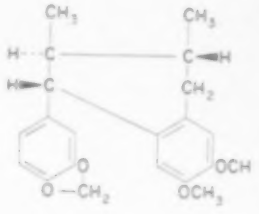
(3) 2:2:I (—)-*Guajakharzsäure*

(a) 2.3-Dimethyl-1.4-bis-[4-hydroxy-3-methoxy-phenyl]-buten-1
(b) 4.4′-Dihydroxy-3.3′-dimethoxy-β8-lignen-7′
(c) (8R)-Guajalignen-7′
Hearon 961; Erdtman 432; Karrer 1168; ferner[6,7]



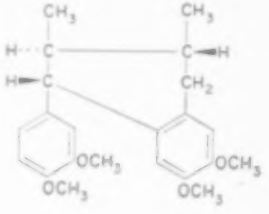
(4) 2:2:I (—)-*Galcatin*

(a) 6.7-Dimethoxy-2.3-dimethyl-1-(3.4-methylendioxy-phenyl)-1.2.3.4-tetrahydro-naphthalin
(b) 3.4-Methylendioxy-3′.4′-dimethoxy-α7.β8.α8′-cyclolignan
(c) 7S.8S.8′R
Hearon 961, 1049; Erdtman 448; Karrer 1173; ferner[6,9]



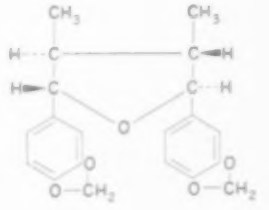
(5) 2:2:I (—)-*Galbulin*

(a) 6.7-Dimethoxy-2.3-dimethyl-1-[3.4-dimethoxy-phenyl]-1.2.3.4-tetrahydro-naphthalin
(b) 3.4.3′.4′-Tetramethoxy-α7.β8.α8′-cyclolignan
(c) (7S.8S.8′R)-Guaja-cyclolignan-dimethyläther
Hearon 1049; Erdtman 448; Karrer 1172; ferner[8–11]



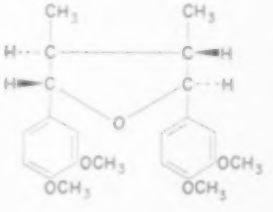
(6) 2:2:II (—)-*Galbacin*

(a) 3.4-Dimethyl-2.5-bis-(3.4-methylendioxy-phenyl)-tetrahydrofuran
(b) (3.4).(3′.4′)-Methylendioxy-7.7′-epoxy-α7.β8.β7′.α8′-lignan
(c) (7S.8S.7′S.8′S)-7.7′-epoxy-piperolignan
Hearon 959, 984; Erdtman 448; Karrer 1160; ferner[8–10,12]

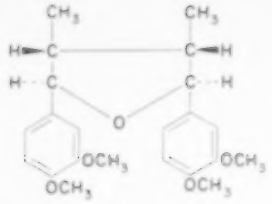


(7) 2:2:II (—)-*Galbelgin*

(a) 3.4-Dimethyl-2.5-bis[3.4-dimethoxy-phenyl]-tetrahydrofuran
(b) 3.4.3′.4′-Tetramethoxy-7.7′-epoxy-α7.β8.β7′.α8′-lignan
(c) (7S.8S.7′S.8′S)-7.7′Epoxy-guajalignan-dimethyläther[8,12]



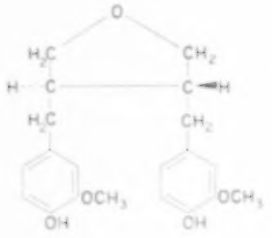
[8] G. K. Hughes u. E. Ritchie, *Austl. J. Chem.* **7**, 104 (1954); *Chem. Abstr.* **49**, 3101 (1955); hier die Substituenten verwechselt).
[9] A. W. Schrecker u. J. L. Hartwell, *J. Amer. Chem. Soc.* **77**, 432 (1955).
[10] A. J. Birch, B. Milligan, E. Smith u. R. N. Speake, *J. Chem. Soc.* 4471 (1958).
[11] B. Carnmalm, *Acta Chem. Scand.* **8**, 1827 (1954).
[12] Die angegebene Konfiguration von 7 und 7′ folgern wir aus der Linksdrehung; s. Olivil, 15) sowie K. Freudenberg u. G. S. Sidhu, *Tetrahedron Letters* Nr. 20, 3 (1960) und Fussnote 25.



identisch mit:

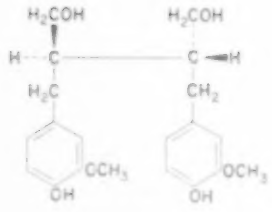
(8) 2:2:II *Galgravin inaktiv, Mesoform*

(a) 3.4-Dimethyl-2.5-bis-[3.4-dimethoxy-phenyl]-tetrahydrofuran
(b) 3.4.3′.4′-Tetramethoxy-7.7′-epoxy-α8.α8′ oder β8.β8′-lignan
(c) 7.7′-Epoxy-guajalignan-dimethyläther
Hearon 986; Erdtman 448; Karrer 1159; ferner.[7–10,18] Die hier angenommene mene trans-Stellung ist bevorzugt wegen der äquatorialen Lage der Benzolringe.



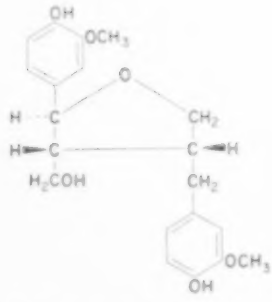
(9) 2:2:II (—)-*Divanillyl-tetrahydrofuran*[14,15]

(a) 3.4-Bis-[4-hydroxy-3-methoxy-benzyl]-tetrahydrofuran
(b) 4.4′-Dihydroxy-3.3′-dimethoxy-9.9′-epoxy-β8.α8′-lignan
(c) (8R.8′R)-9.9′-Epoxy-guajalignan



(10) 2:2:II (—)-*Seco-isolariciresinol*[16–18]

(a) 2.3-Bis-hydroxymethyl-1.4-bis-[4-hydroxy-3-methoxy-phenyl]-butan
(b) 4.9.4′.9′-Tetrahydroxy-3.3′-dimethoxy-β8.α8′-lignan
(c) (8R.8′R)-9.9′-Dihydroxy-guajalignan



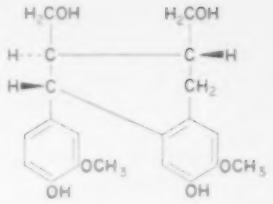
(11) 2:2:III (+)-*Lariciresinol*

(a) 3-Hydroxymethyl-2-(4-hydroxy-3-methoxy-phenyl)-4-(4-hydroxy-3-methoxy-benzyl)-tetrahydrofuran
(b) 4.4′.9-Trihydroxy-3.3′-dimethoxy-7.9′-epoxy-β7.α8.α8′-lignan
(c) (7S.8R.8′R)-7.9′-Epoxy-9-hydroxy-β7-guajalignan
Hearon 987; Erdtman 436; Karrer 1158; ferner[18]

[7] J. G. Blears u. R. D. Haworth, *J. Chem. Soc.* 1985 (1958).
[8] R. D. Haworth u. D. Woodcock, *J. Chem. Soc.* 1054 (1939)
[9] K. Freudenberg u. L. Knof, *Chem. Ber.* **90**, 2857 (1957).
[10] L. H. Briggs, R. C. Cambie u. J. L. Hoare, *Tetrahedron Letters* Nr. 4, 14 (1959).
[11] K. Freudenberg u. K. Weinges, *Tetrahedron Letters* Nr. 17, 19 (1959);
[12] K. Weinges, *Tetrahedron Letters* Nr. 20, 1 (1960).
[13] R. D. Haworth u. L. Wilson, *J. Chem. Soc.* 71 (1950).
[14] F. v. Bruchhausen und H. Gerhard, *Ber. Dtsch. Chem. Ges.* **72**, 830 (1939).

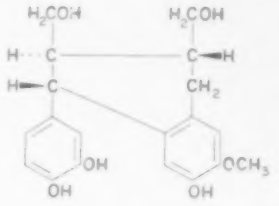
(12) 2:2:III (+)-*Iso-lariciresinol*[18,19]

(a) 7-Hydroxy-6-methoxy-2.3-bis-hydroxymethyl-1-(4-hydroxy-3-methoxy-phenyl)-1.2.3.4-tetrahydronaphthalin
(b) 4.9.4′.9′-Tetrahydroxy-3.3′-dimethoxy-α7.β8.α8′-cyclolignan
(c) (7S.8R.8′R)-9.9′-Dihydroxy-guaja-cyclolignan



(13) 2:2:III (+)-*Isotaxiresinol*

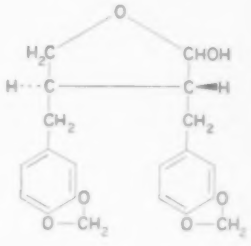
(a) 7-Hydroxy-6-methoxy-2.3-bis-hydroxymethyl-1-(3.4-dihydroxyphenyl)-1.2.3.4.-tetrahydro-naphthalin
(b) 3.4.9.4′9′.-Pentahydroxy-3′-methoxy-α7.β8.α8′-cyclolignan
(c) 7S.8R.8′R
Hearon 1045; Erdtman 442; Karrer 1170



(14) 2:2:III (−)-*Cubebin*

(a) 5-Hydroxy-3.4-bis-[3.4-methylendioxy-benzyl]-tetrahydrofuran
(b) (3.4).(3′.4′)-Bis-methylendioxy-9′-hydroxy-9.9′-epoxy-β8.α8′-lignan
(c) (8R.8′R)-9′-Hydroxy-9.9′-epoxy-piperolignan
Hearon 980; Erdtman 435; Karrer 1162

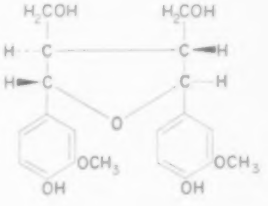
Das durch Reduktion entstehende Diol dreht links.[20] Daraus folgern wir, dass (−)-Cubebin dieselbe Konfiguration hat wie (−)-Seco-isolariciresinol.



(15) 2:2:IV (−)-*Olivil*

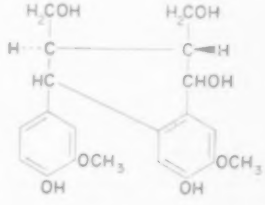
(a) 3.4-Bis-hydroxymethyl-2.5-bis-(4-hydroxy-3-methoxy-phenyl)-tetrahydrofuran
(b) 4.9.4′.9′-Tetrahydroxy-3.3′-dimethoxy-7.7′-epoxy-β8.α8′-lignan, wahrscheinlich α7.β7′
(c) (7S.8R.7′S.8′R)-9.9′-Dihydroxy-7.7′-epoxy-guajalignan
Hearon 983; Erdtman 436; Karrer 1161; ferner[12]

Die Konfiguration von 7 und 7′ erschliessen wir aus der Drehung.



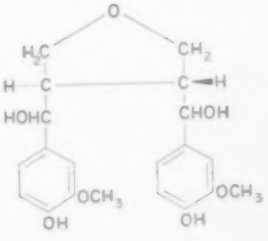
(16) 2:2:IV (+)-*Iso-olivil*

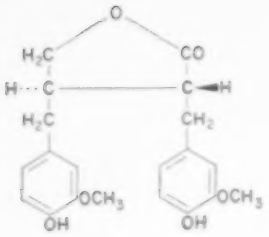
(a) 7-Hydroxy-6-methoxy-2.3-bis-hydroxymethyl-1-(4-hydroxy-3-methoxy-phenyl)-1.2.3.4-tetrahydronaphthalin
(b) 4.9.4′.7′.9′-Pentahydroxy-3.3′-dimethoxy-β8.α8′-cyclolignan
(c) (8R.8′R)-9.7′.9′-Trihydroxy-guaja-cyclolignan
Hearon 1043; Erdtman 444; Karrer 1171



(17) 2:2:IV (−)-*Liovil*[15,17]

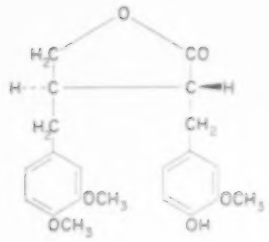
(a) 3.4-Bis-[4.α-dihydroxy-3-methoxy-benzyl]-tetra-hydrofuran
(b) 4.7.4′.7′-Tetrahydroxy-3.3′-dimethoxy-9.9′-epoxy-β8.α8′-lignan
(c) (8R.8′R′)-7.7′-Dihydroxy-9.9′-epoxy-guajalignan





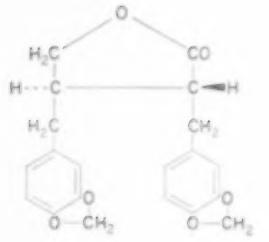
(18) 2:2:IV (−)-*Matairesinol*

(a) 2.3-Bis-[4-hydroxy-3-methoxy-benzyl]-butanolid-(4.1)
(b) 4.4′-Dihydroxy-3.3′-dimethoxy-β8.α8′-lignan-olid-(9.9′)
(c) (8R.8′R)-Guaja-lignan-olid-(9.9′)
Hearon 971; Erdtman 433 ; Karrer 1163



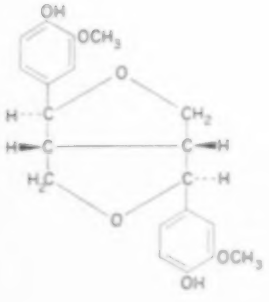
(19) 2:2:IV (−)-*Arctigenin, Matairesinol-4-methyläther*

(a) 2-[4-Hydroxy-3-methoxy-benzyl]-3-[3.4-dimethoxy-benzyl]-butanolid-(4.1)
(b) 4′-Hydroxy-3.4.3′-trimethoxy-lignan-olid-(9.9′)
(c) (8R.8′R)-4-Methyl-guajalignan-olid-(9,9′)
Hearon 2053; Erdtman 434; Karrer 1165



(20) 2:2:IV (−)-*Hinokinin*

(a) 2.3-Bis-[3.4-methylendioxy-benzyl]-butanolid
(b) (3.4).(3.′4′)-Bis-methylendioxy-β8.α8′-lignan-olid-(9.9′)
(c) (8R.8′R)-Piperolignanolid-(9.9′)
Hearon 966; Erdtman 436; Karrer 1166



(21) 2:2:IV (+)-*Pinoresinol*

(a) 2.6-Bis-[4-hydroxy-3-methoxy-phenyl]-3.7-dioxa-bicyclo-[3.3.0]-octan
(b) 4.4′-Dihydroxy-3.3′-dimethoxy-(7.9′).(9.7′)-bis-epoxy-β7.α8.β7′.α8′-lignan
(c) (7S.8R.7′S.8′R)-(7.9′).(9.7′)-Bis-epoxy-guajalignan
Hearon 991; Erdtman 438; Karrer 1150; ferner[7,9,10,21–28]

(22) 2:2:IV (+)-*Pinoresinol-dimethyläther* = (+)-*Eudesmin* 7S.8R.7′S.8′R[27,28]

(23) 2:2:IV (−)-*Pinoresinol-dimethyläther* = (−)-*Eudesmin* 7R.8S.7′R.8′S
Hearon 995; Erdtman 439; Karrer 1153

[21] B. C. Carnmalm, H. Erdtman u. Z. Pelchowicz, *Acta Chem. Scand.* **9**, 1111 (1955).
[22] H. Erdtman u. Z. Pelchowicz, *Chem. & Ind.* 567 (1953).
[23] E. W. Lund, *Acta Chem. Scand.* **14**, 496 (1960).
[24] K. Freudenberg u. G. S. Sidhu, *Tetrahedron Letters* Nr. 20, 3 (1960).
[25] K. Freudenberg, u. G. S. Sidhu, *Chem. Ber.* **94**, 851 (1961).
[26] M. Beroza, *J. Amer. Chem. Soc.* **78**, 5082 (1956).
[27] E. Dryselius u. B. Lindberg, *Acta Chem. Scand.* **10**, 445 (1956).
[28] G. Combes, D. Billet u. C. Mentzer, *Bull. Soc. Chim. Fr.* 2014 (1959).

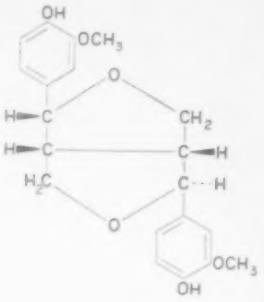
(24) 2:2:IV (+)-*Epipinoresinol*

(a) wie Pinoresinol

(b) 4.4′-Dihydroxy-3.3′-dimethoxy-(7.9′).(9.7′)-bis-epoxy-α7.α8.β7′.α8′-lignan

(c) (7R.8R.7′S.8′R)-7.9′.9.7′-Bis-epoxy-guajalignan

Hearon 993; Erdtman 438; neuere Literatur s. Pinoresinol



(25) 2:2:IV (−)-*Epipinoresinol* = (−)-*Symplocosigenol*

7S.8S.7′R.8′S

Hearon 1000; Erdtman 439

(26) 2:2:IV (+)-*Epipinoresinol-monomethyläther* = (+)-*Phillygenin*

7R.8R.7′S.8′R

Hearon 994; Erdtman 430; Karrer 1151/2

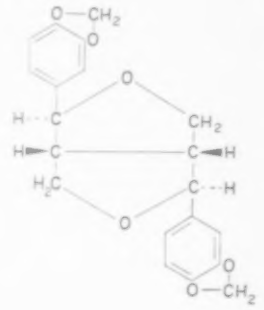
(27) 2:2:IV (+)-*Sesamin*

(a) 2.6-Bis-[3.4-methylendioxy-phenyl]-3.7-dioxa-bicyclo-[3.3.0]-octan

(b) (3.4).(3′.4′)-Bis-methylendioxy-(7.9′).(9.7′)-bis-epoxy-β7.α8.β7′.α8′-lignan

(c) (7S.8R.7′S.8′R)-(7.9′).(9.7′)-Bis-epoxy-piperolignan

Hearon 996; Erdtman 441; Karrer 463; neuere Literatur wie (+)-Pinoresinol



(28) 2:2:IV (−)-*Sesamin*

7R.8S.7′R.8′S

Hearon 996; Erdtman 441; Karrer 463

(29) 2:2:IV (±)-*Sesamin* = *Fagarol*

7S.8R.7′S.8′R + 7R.8S.7′R.8′S

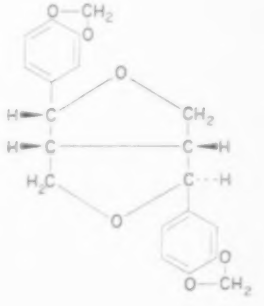
Hearon 996; Erdtman 442; Karrer 463; ferner[21]

(30) 2:2:IV (+)-*Asarinin* = (+) *Episesamin*

(a) wie Sesamin

(b) (3.4).(3′.4′)-Bis-methylendioxy-(7.9′).(9.7′)-bis-epoxy-α7.α8.β7′.α8′-lignan

(c) (7R.8R.7′S.8′R)-(7.9′).(9.7′)-Bis-epoxy-piperolignan



(31) 2:2:IV (−)-*Asarinin* = (−)-*Episesamin*

(a) wie Sesamin

(b) (3.4).(3′.4′)-Bis-methylendioxy-(7.9′).(9.7′)-bis-epoxy-β7.β8.α7′.β8′-lignan

(c) (7S.8S.7′R.8′S)-(7.9′).(9.7′)-Bis-epoxy-piperolignan

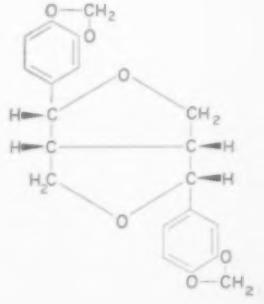
Hearon 998; Erdtman 441; Karrer 1155; neuere Literatur wie (+)-Pinoresinol

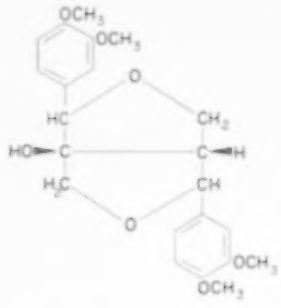
(32) 2:2:IV (+)-*Epiasarinin* = *Diasesamin*[24–26] (*Kunstprodukt*)

(a) wie Sesamin

(b) (3.4).(3′.4′)-Bis-methylendioxy-(7.9′).(9.7′)-bisepoxy-α7.α8.α7′α8′-lignan

(c) (7R.8R.7′R.8′R)-(7.9′).(9.7′)-Bis-epoxy-piperolignan





(33) 2:2:V *Gmelinol* = (+)-8-*Hydroxy-pinoresinol-dimethyläther*

(a) 2.6-Bis-(3.4-dimethoxy-phenyl)-3.7-dioxa-bicyclo-[3.3.0]-octanol-1

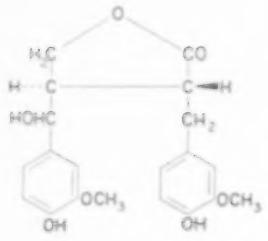
(b) 3.4.3′.4′-Tetramethoxy-8-hydroxy-(7.9′).(9.7′)-bis-epoxy-α8.α8′-lignan

(c) (8S.8′R)-8-Hydroxy-4.4′-dimethyl-7.9′.9.7′-bis-epoxy-guajalignan

Hearon 1000; Erdtman 440; Karrer 1156

OH-(8) und H-(8′) müssen *cis*-Stellung haben. Wird zu Isogmelinol (+30°, $CHCl_3$) isomerisiert. Aus Gründen der Drehung entspricht (+)-Gmelinol wahrscheinlich dem (+)-Epipinoresinol, (+)-Isogmelinol dem (+)-Pinoresinol.

(34) 2:2:V (−)-Hydroxy-matairesinol[15]

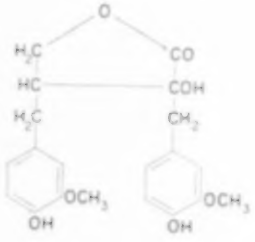


(35) 2:2:V *Allo-hydroxy-matairesinol*[15]

(a) 2-[4-Hydroxy-3-methoxy-benzyl]-3-[(4-hydroxy-3-methoxy-phenyl)-hydroxymethyl]-butanolid-(4.1)

(b) 4.7.4′-Trihydroxy-3.3′-dimethoxy-β8.α8′-lignan-olid-(9.9′)

(c) (8R.8′R)-7-Hydroxy-guajalignan-olid-(9.9′)

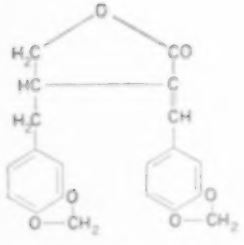


(36) 2:2:V (−)-*Pinopalustrin*[29]

(a) 2-Hydroxy-2.3-bis-[4-hydroxy-3-methoxy-benzyl]-butanolid-(4.1)

(b) 4.4′.8′-Trihydroxy-3.3′-dimethoxy-lignan-olid-(9.9′)

(c) 8′-Hydroxy-guajalignan-olid-(9.9′)



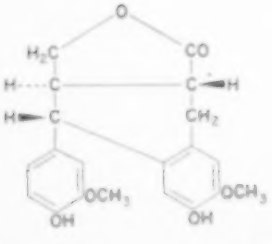
(37) 2:2:V (−)-*Savinin*

(a) 3-[3.4-Methylen-dioxy-benzyl]-2-[3.4-methylendioxy-benzyliden]-butanolid-(4.1)

(b) (3.4).(3′.4′)-Bis-methylendioxy-lignen-7′-olid-(9.9′)

(c) Pipevolignen-7′-olid-(9.9′)

Hearon 969; Erdtman 443, 448; Karrer 1169



(38) 2:2:V (−)-*Conidendrin*

(a) 7-Hydroxy-6-methoxy-2-hydroxymethyl-1-(4-hydroxy-3-methoxy-phenyl)-1.2.3.4-tetrahydro-naphthalin-3-carbonsäure-lacton

(b) 4.4′-Hydroxy-3.3′-methoxy-α7.β8.α8′-cyclo-lignan-olid-(9.9′)

(c) (7S.8R.8′R)-guaja-cyclolignan-olid-(9.9′)

Hearon 1031; Erdtman 442; Karrer 1175

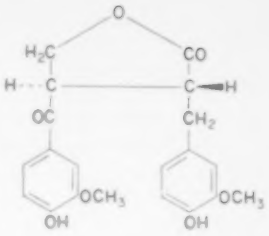
[29] B. Carnmalm, *Svensk Kem. Tidskr.* **71**, 440 (1959).

(39) 2:2:VI (+)-*Oxo-matairesinol*[15]

(a) 2-[4-Hydroxy-3-methoxy-benzyl]-3-[4-hydroxy-3-methoxy-benzoyl]-butanolid-(4.1)

(b) 4.4′-Dihydroxy-3.3′-dimethoxy-7-oxo-β8.α8′-lignan-olid (9.9′)

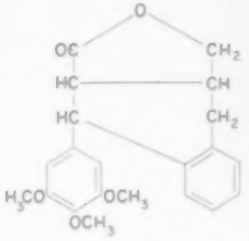
(c) (8R.8′R)-7-Oxo-guajalignan-olid-(9.9′)



(40) 3:0:V 3-*Hydroxymethyl*-1-(3.4.5-*trimethoxy-phenyl*)-1.2.3.4-*tetrahydronaphthalin*-2-*carbonsäure-lacton*

(b) 3.4.5-Trimethoxy-cyclolignan-olid-(9′.9)

Karrer 1174; ferner[30]



(41) 3:2:V (−)-*Dehydroxy-podophyllotoxin*

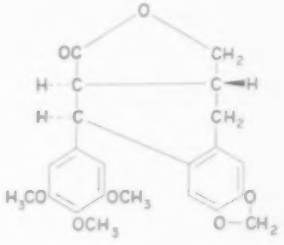
Silicicolin, Anthricin, Hernandion

(a) 6.7-Methylendioxy-3-hydroxymethyl-1-[3.4.5-trimethoxy-phenyl]-1.2.3.4-tetrahydronaphthalin-2-carbonsäure-lacton

(b) 3.4.5-Trimethoxy-3′.4′-methylendioxy-β7.β8.α8′-cyclolignan-olid-(9′.9)

(c) 7R.8R.8′R

Hearon 1027; Erdtman 444; Karrer 1176

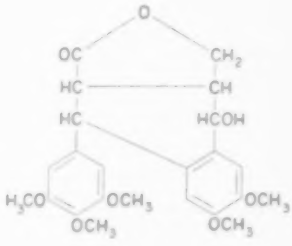


(42) 3:2:VI (−)-*Sikkimotoxin*

(a) 4-Hydroxy-6.7-dimethoxy-3-hydroxymethyl-1-[3.4.5-trimethoxy-phenyl]-1.2.3.4-tetrahydronaphthalin-2-carbonsäure-lacton

(b) 3.4.5.3′.4′-Pentamethoxy-7′-hydroxy-cyclolignan-olid-(9′.9)

Hearon 1057; Erdtman 445; ferner[31]



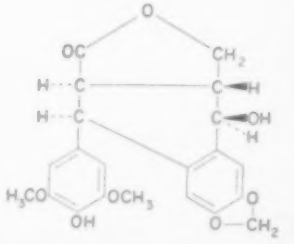
(43) 3:2:VI (−)-*Demethyl-podophyllotoxin*

(a) 4-Hydroxy-6.7-methylendioxy-3-hydroxymethyl-1-[4-hydroxy-3.5-dimethoxy-phenyl]-1.2.3.4-tetrahydronaphthalin-2-carbonsäure-lacton

(b) 4.7′-Dihydroxy-3.5-dimethoxy-3′.4′-methylendioxy-β7.β8.β7′.α8′-cyclolignan-olid-(9′.9)

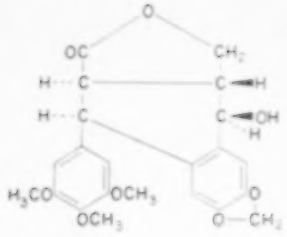
(c) 7R.8R.7′R.8′R

Hearon 1015; Erdtman 447; Karrer 1184



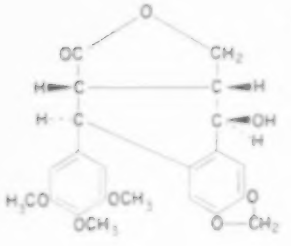
[30] Ch. Hata, *J. Chem. Soc. Japan* **63**, 1540 (1942); *Chem. Abstr.* **41**, 2917 (1947).

[31] R. Chatterjee u. S. C. Chakravarti, *J. Amer. Pharm. Assoc. Sci. Ed.* **41**, 415 (1952); *Chem. Abstr.* **47**, 5920 (1953); R. Chatterjee u. D. K. Datta, *Ind. J. Physiol. Allied Sci.* **4**, 61 (1950).



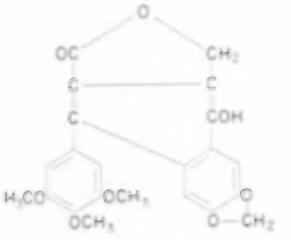
(44) 3:2:VI (−)-*Podophyllotoxin*

(a) 4-Hydroxy-6.7-methylendioxy-3-hydroxymethyl-1-[3.4.5-trimethoxy-phenyl]-1.2.3.4-tetrahydronaphthalin-2-carbonsäure-lacton
(b) 3.4.5-Trimethoxy-3′.4′-methylendioxy-7′-hydroxy-β7.β8.β7′.α8′-cyclolignan-olid-(9′.9)
(c) 7R.8R.7′R.8′R
Hearon 1015; Erdtman 466; Karrer 1182; ferner[32]



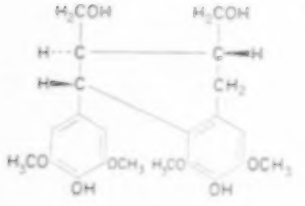
(45) 3:2:VI (+)-*Picropodophyllin* (*Kunstprodukt aus Podophyllotoxin*)

(a) 4-Hydroxy-6.7-methylendioxy-3-hydroxymethyl-1-[3.4.5-trimethoxy-phenyl]-1.2.3.4-tetrahydronaphthalin-2-carbonsäure-lacton
(b) 3.4.5-Trimethoxy-3′.4′-methylendioxy-7′-hydroxy-β7.α8.β7′α8′-cyclolignan-olid-(9′.9)
(c) 7R.8S.7′R.8′R
Hearon 1019; Erdtman 447; Karrer 1180 ; ferner[32,33]



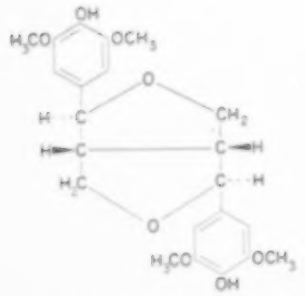
(46) 3:2:VIII *Dehydro-podophyllotoxin*

(a) 4-Hydroxy-6.7-methylendioxy-2-hydroxymethyl-1-[3.4.5-trimethoxy-phenyl]-naphthalin-2-carbonsäure-lacton
(b) 3.4.5-Trimethoxy-3′.4′-methylendioxy-7′-hydroxy-cycloligna-dien-7.7′-olid-(9′.9)
Hearon 1030; Karrer 1186; ferner[33]



(47) 3:3:III (+)-*Dimethoxy-isolariciresinol*[17,34] ((+)-*Lyoniresinol*)

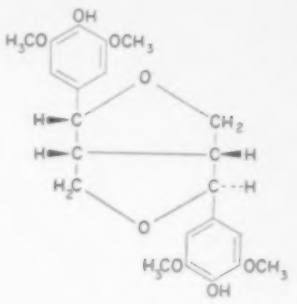
(a) 7-Hydroxy-6.8-dimethoxy-2.3-bis-hydroxymethyl-1-(4-hydroxy-3.5-dimethoxy-phenyl)-1.2.3.4-tetrahydronaphthalin
(b) 4.9.4′.9′-Tetrahydroxy-3.5.3′.5′-tetramethoxy-α7.β8.α8′ cyclolignan
(c) (7S.8R.8′R)-9.9′-Dihydroxy-syringa-cyclolignan



(48) 3:3:IV (+)-*Syringaresinol* (Lirioresinol C)[25,33]

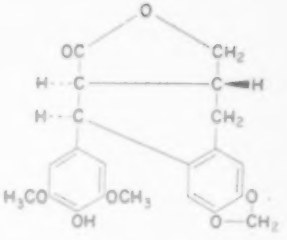
(a) 2.6-Bis-[4-hydroxy-3.5-dimethoxy-phenyl]-3.7-dioxa-bicyclo-[3.3.0]-octan
(b) 4.4′-Dihydroxy-3.5.3′,5′-tetramethoxy-(7.9′).(9.7′)-bis-epoxy-β7.α8.β7′.α8′-lignan
(c) (7S.8R.7′S.8′R)-(7.9′).(9.7′)-Bis-epoxy-syringa-lignan

[30] A. v. Wartburg, E. Angliker u. J. Renz, *Helv. Chim. Acta* **40**, 1331 (1957).
[33] Chr. Jörgensen u. H. Kofod, *Acta Chem. Scand.* **8**, 941 (1954); **9**, 346 (1955).
[34] N. Yasue u. Y. Kato, *Yakugaku, Zasshi* **80**, 1013 (1960); *Chem. Pharm. Bull.* **8**, 169 (1960).
[35] E. E. Dickey, *J. Org. Chem.* **23**, 179 (1958).



(49) 3:3:IV (+)-*Episyringaresinol*[35,35]
(Lirioresinol A)

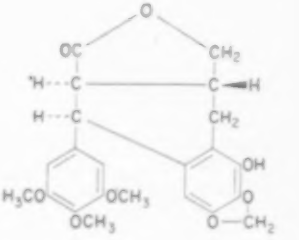
(a) wie (+)-Syringaresinol
(b) 4.4′-Dihydroxy-3.5.3′.5′-tetramethoxy-(7.9′).(9.7′)-bis-epoxy-α7.α8.β7′α8′-lignan
(c) (7R.8R.7′S.8′R)-(7.9′).(9.7′)-Bis-epoxy-syringa-lignan



(50) 3:3:V α-(−)-*Peltatin*

(a) 5-Hydroxy-6.7-methylendioxy-3-hydroxymethyl-1-(4-hydroxy-3.5-dimethoxy-phenyl)-1.2.3.4-tetrahydro-naphthalin-2-carbonsäure-lacton
(b) 4.2′-Dihydroxy-3.5-dimethoxy-3′.4′-methylendioxy-β7.β8.α8′-cyclolignan-olid-(9′.9)
(c) 7R.8R.8′R

Hearon 1022, 1026; Erdtman 445, 448; Karrer 1177; ferner[32,36]



(51) 3:3:V β-(−)-*Peltatin*

(a) 5-Hydroxy-6.7-methylendioxy-3-hydroxymethyl-1-(3.4.5-trimethoxy-phenyl)-1.2.3.4-tetrahydronaph-thalin-2-carbonsäure-lacton
(b) 2′-Hydroxy-3.4.5-trimethoxy-3′.4′-methylendioxy-β7.β8.α8′-cyclolignan-olid-(9′.9)
(c) 7R.8R.8′R

Hearon 1022; Erdtman 445; Karrer 1179; ferner[32,36]

[36] A. Stoll, A. v. Wartburg u. J. Renz, *J. Amer. Chem. Soc.* **77**, 1710 (1955).

VERZEICHNIS

Name	Nr.	Klassifizierung
Allohydroxymatairesinol	35	2:2:V
Anthricin	41	3:2:V
Arctigenin	19	2:2:IV
Asarinin	30, 31	2:2:IV
Conidendrin	38	2:2:V
Cubebin	14	2:2:III
Dehydro-podophyllotoxin	46	3:2:VIII
Dehydroxy-podophyllotoxin	41	3:2:V
Demethyl-podophyllotoxin	43	3:2:VI
Diasesamin	32	2:2:IV
Dimethoxy-isolariciresinol	47	3:3:III
Dihydro-guajakharzsäure-dimethyläther	2	2:2:0
Divanillyl-tetrahydrofuran	9	2:2:II
Epiasarinin	32	2:2:IV
Epipinoresinol	24, 25	2:2:IV
Epipinoresinol-monomethyläther	26	2:2:IV
Episesamin	30, 31	2:2:IV
Episyringaresinol	49	3:3:IV
Eudesmin	22, 23	2:2:IV
Fagarol	29	2:2:IV
Galbacin	6	2:2:II
Galbelgin	7	2:2:II
Galbulin	5	2:2:I
Galcatin	4	2:2:I
Galgravin	8	2:2:II
Gmelinol	33	2:2:V
Guajakharzsäure	3	2:2:I
Hernandion	41	3:2:V
Hinokinin	20	2:2:IV
Hydroxy-matairesinol	34	2:2:V
Isolariciresinol	12	2:2:III
Iso-olivil	16	2:2:IV
Isotaxiresinol	13	2:2:III
Lariciresinol	11	2:2:III
Liovil	17	2:2:IV
Lirioresinol	48, 49	3:3:IV
Lyoniresinol	47	3:3:III
Matairesinol	18	2:2:IV
Matairesinol-4-methyläther	19	2:2:IV
Nordihydro-guajakharzsäure	1	2:2:0
Olivil	15	2:2:IV
Oxo-matairesinol	39	2:2:VI
Peltatin	50, 51	3:3:V
Phillygenin	26	2:2:IV
Picropodophyllin	45	3:2:VI
Pinopalustrin	36	2:2:V
Pinoresinol	21	2:2:IV
Pinoresinol-dimethyläther	22, 23	2:2:IV
Podophyllotoxin	44	3:2:VI
Savinin	37	2:2:V
Seco-isolariciresinol	10	2:2:II
Sesamin	27, 28, 29	2:2:IV
Sikkimotoxin	42	3:2:VI
Silicicolin	41	3:2:V
Symplocosigenol	25	2:2:IV
Syringaresinol	48	3:3:IV
Trimethoxyphenyl-oxymethyl-tetra-hydro-naphthalin-carbonsäure-lacton	40	3:0:V

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Tetrahedron, 1961, Vol. 15, pp. 129 to 131. Pergamon Press Ltd. Printed in Northern Ireland

CHEMICAL EXAMINATION OF *WEDELIA CALENDULACEAE*—IV

SYNTHETIC ANALOGUES OF WEDELOLACTONE

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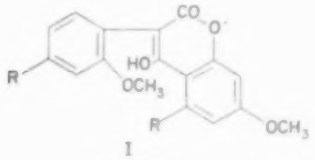
(*Received* 20 *March* 1961)

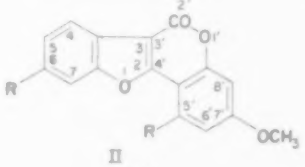
Abstract—The syntheses of 7′-methoxy- and 5′,7′,6-trimethoxy-coumarino(3′,4′:3,2)coumarones (IIa and IIb) are described.

SOME time ago we had isolated a crystalline substance named wedelolactone from the fresh leaves of *Wedelia calendulaceae*.[1] The structure of this compound as 5′,5,6-trihydroxy-7′-methoxy-coumarino(3′,4′:3,2)coumarone was proved by degradation[2] as well as by synthesis of its tri-O-methyl ether.[3] Subsequently Bickoff *et al.*,[4] reported the isolation from ladino clover of an estrogenic substance, coumestrol which was shown to be 6,7′-dihydroxycoumarino(3′,4′:3,2)coumarone by degradation as well as by synthesis. It was of interest to prepare some analogous compounds for comparative pharmacological tests,[5] so that the structural features necessary for estrogenic activity may be revealed. As part of the programme, we have synthesised 7′-methoxy- and 5′,7′,6-trimethoxycoumarino(3′,4′:3,2)coumarones (IIa and IIb) by the route employed in the synthesis of tri-O-methylwedelolactone.[3]

Condensation of 2-hydroxy-4-methoxyphenyl *o*-methoxybenzyl ketone[6] with diethyl carbonate and pulverized sodium afforded in satisfactory yield 4-hydroxy-7-methoxy-3(*o*-methoxyphenyl)-coumarin (Ia). The latter, on treatment with pyridine



I
a: R = H
b: R = OCH_3



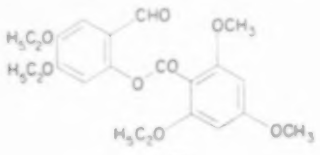
II
a: R = H
b: R = OCH_3

hydrochloride followed by subsequent methylation, gave 7′-methoxycoumarino-(3′,4′:3,2)coumarone (IIa). Likewise 5′,7′,6-trimethoxycoumarino(3′,4′:3,2)coumarone (IIb) was obtained from the corresponding coumarin (Ib) by fusion with pyridine hydrochloride followed by methylation.

In an earlier publication,[2] we had reported the reduction of the compound III by

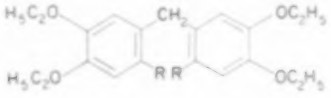
[1] T. R. Govindachari, K. Nagarajan and B. R. Pai, *J. Chem. Soc.* 629 (1956).
[2] T. R. Govindachari, K. Nagarajan, B. R. Pai and P. C. Parthasarathy, *J. Chem. Soc.* 545 (1957).
[3] T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *J. Chem. Soc.* 548 (1957).
[4] E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. De Eds, *Science* **126**, 969 (1957).
[5] E. M. Bickoff, A. L. Livingston and A. N. Booth, *Arch. Biochem. & Biophys.* **88**, 262 (1960).
[6] P. K. Grover and T. R. Seshadri, *Proc. Indian. Acad. Sci.* **38**, 122 (1953).

lithium aluminium hydride. One of the products isolated by decomposing the reaction mixture with dilute sulphuric acid was considered to be 3,4-diethoxy-6-hydroxybenzyl alcohol (IV). However, the benzoate of the compound on treatment with alkali and diethyl sulphate gave a product identical with 2,4,5:2′,4′,5′-hexaethoxydiphenylmethane (Vb), prepared from 2,4,5-triethoxybenzaldehyde by reduction with sodium borohydride followed by treatment with acid. Hence the reduction



III

IV



V

a : R = OH
b : R = OC_2H_5

product should actually be 3,4,3′,4′-tetraethoxy-6,6′-dihydroxydiphenylmethane (Va) produced by the action of acid[7] on the initially formed alcohol (IV) during the process of isolation.

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured using a Beckmann Model DU Spectrophotometer.

4-Hydroxy-7-methoxy-3(o-methoxyphenyl)coumarin (Ia)

2-Hydroxy-4-methoxyphenyl *o*-methoxybenzyl ketone (2 g) in diethyl carbonate (25 ml) containing pulverized sodium (1·5 g) was warmed on a water-bath for 40 min. The granular sodium salt that separated was treated with a small volume of methanol to decompose excess sodium. Water (50 ml) was added, and the solution after repeated extraction with ether, made acidic to congo-red. The *coumarin* (1·8 g) separated out as a white solid, which on crystallization from methanol was obtained as colourless needles, m.p. 178°, λ_{max} 313 mμ (log ε 4·3) (Found: C, 68·6; H, 4·8. $C_{17}H_{14}O_5$ requires: C, 68·5; H, 4·7%).

The *acetate*, prepared by use of acetic anhydride and pyridine at 100° for 1/2 hr, formed colourless needles from acetic acid, m.p. 163° (Found: C, 67·5; H, 4·7. $C_{19}H_{16}O_6$ requires: C, 67·1; H, 4.7%).

The *methyl ether*, obtained by refluxing the coumarin (0·2 g) with methyl iodide (1 ml) and potassium carbonate (1 g) in dry acetone (5 ml) for 1 hr, had m.p. 119°, colourless cubes from aqueous methanol. (Found: C, 69·0; H, 5·1. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·1%).

7′-Hydroxycoumarino(3′,4′:3,2)coumarone

The foregoing hydroxycoumarin (1 g) was heated with dry pyridine hydrochloride (8 g) at 220° in an atmosphere of nitrogen for 1 hr. The reaction mixture was then cooled and treated with water (20 ml). A brown semi-crystalline alkali-soluble mass separated on leaving in the ice-chest overnight. This was collected, washed with water and dried. After sublimation at 200°/1 mm and crystallization from methanol, *7′-hydroxycoumarino-(3′,4′:3,2)coumarone* (0·5 g) was obtained as needles, m.p. 285°, λ_{max} 240, 295, 330 mμ (log ε 4·15, 3·95, 4·32) (Found: C, 71·6; H, 3·4. ($C_{18}H_{10}O_4$ requires: C, 71·4; H, 3·2%).

[7] T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *J. Chem. Soc.* 912 (1958).

The *acetate*, prepared by use of acetic anhydride and pyridine in the cold, was obtained as needles, m.p. 105–106°, from acetic acid. (Found: C, 69·2; H, 3·4. $C_{17}H_{10}O_5$ requires: C, 69·4; H, 3·4%).

7′-Methoxycoumarino(3′,4′:3,2)coumarone (IIa)

The above hydroxylactone (0·5 g) was refluxed with methyl iodide (2 ml), actone (20 ml) and potassium carbonate (2 g) for 4 hr. After removal of acetone, water was added and the residue was washed with alcohol and then crystallized from acetic acid to yield colourless needles of *7′-methoxy coumarino-(3′,4′:3,2)coumarone* (0·3 g), m.p. 195–196°, λ_{max} 240, 295, 330 mμ (log ε 4·2, 3·95, 4·35) (Found: C, 72·2; H, 3·5. $C_{16}H_{10}O_4$ requires: C, 72·2; H, 3·8%).

5′,7′,6-Trimethoxycoumarino(3′,4′:3,2)coumarone (IIb)

2-Hydroxy-4,6-dimethoxyphenyl 2,4-dimethoxybenzyl ketone. 2,4,6-Trihydroxyphenyl 2,4-dimethoxybenzyl ketone (1 g), methyl sulphate (0·9 g), potassium carbonate (3 g) and acetone (25 ml) were heated on a water-bath for 5 hr. The residue (1 g), after evaporation of the solvent, yielded *the ketone* as colourless prisms from alcohol, m.p. 137–138° (Found: C, 65·3; H, 6·1. $C_{18}H_{20}O_6$ requires: C, 65·0; H, 6·0%).

4-Hydroxy-5,7-dimethoxy-3(2,4-dimethoxyphenyl)coumarin (Ib)

Cyclization of the above ketone (1 g) with diethyl carbonate (20 ml) and sodium dust (1 g) during 1 hr, gave the *coumarin* (0·8 g) which separated as needles from acetic acid, m.p. 227°, λ_{max} 317 mμ (log ε 4·22) (Found: C, 63·8; H, 5·2. $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·0%).

The *methyl ether* (0·1 g), prepared by the usual procedure, was obtained from aqueous alcohol as needles, m.p. 171° (Found: C, 64·7; H, 5·6. $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4%).

5′,7′,6-Trimethoxycoumarino(3′,4′:3,2)coumarone (IIb)

The foregoing hydroxycoumarin (0·1 g) was heated with dry pyridine hydrochloride (3 g) at 250° in a current of nitrogen for ½ hr, cooled, and treated with water. The brown solid that separated was methylated with methyl iodide in the usual manner, to yield, *5′,7′,6-trimethoxycoumarino(3′,4′:3,2) coumarone* (50 mg), crystallizing in needles from acetic acid, m.p. 230°, λ_{max} 250, 345 mμ (log ε 4·27, 4·37) (Found: C, 66·2; H, 4·1. $C_{19}H_{14}O_6$ requires: C, 66·3; H, 4·3%).

2,4,5:2′,4′,5′-Hexaethoxydiphenylmethane (Vb)

The dibenzoate[2] (20 mg) was warmed on the water-bath with aqueous potassium hydroxide (1 g in 10 ml) for 1 hr, and to the resulting alkaline solution was added diethyl sulphate (1 ml) with shaking and warming. The reaction mixture was made distinctly alkaline to litmus and left overnight in the ice-chest. *2,4,5:2′,4′,5′-Hexaethoxydiphenylmethane* separated out as needles from methanol, m.p. and mixed m.p. 93°, with an authentic specimen prepared as below:

2,4,5-Triethoxybenzaldehyde (0·5 g) in warm methanol (10 ml) was treated with sodium borohydride (0·2 g) with occasional shaking. Next morning, the reaction mixture was rendered acidic with dil 4 N HCl (20 ml) and the gummy material that separated solidified on digesting with alcohol to yield *2,4,5:2′,4′,5-hexaethoxydiphenylmethane*, crystallizing in needles from alcohol, m.p. 93° (Found: C, 69·7; H, 8·4. $C_{25}H_{36}O_6$ requires: C, 69·4; H, 8·3%).

Acknowledgement—We are thankful to Mr. S. Selvavinayakam for the microanalyses reported here. This work was carried out during the tenure of a Government of India Research Scholarship held by one of us (P. C. P.).

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ECHITAMINE

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(*Received* 6 *March* 1961)

Abstract—Results from degradation studies on echitamine, the alkaloid from *Alstonia scholaris*, are discussed.

ALTHOUGH the alkaloid echitamine was isolated[1] nearly a century ago, the first reliable data on this alkaloid were provided by Goodson and Henry[2] who prepared and analysed several crystalline derivatives and furnished evidence for the presence of an indole ring and a carbomethoxy group. There has been a tremendous upsurge of interest recently on the structure of echitamine as evidenced by the spate of publications on this problem during the last two years.[3-6] We have been carrying out studies on echitamine for sometime and parts of our work have been published already in the form of brief communications.[7] Two contrary views emerge from the work carried out in different laboratories, one that echitamine chloride has an N_a—C—N_b system[3,7] and the other that it has a β-type dihydroindole structure.[4,5] The issue has now been settled by determination of structure by the X-ray method (*vide infra*). Under these circumstances we wish to present in this paper full details of our work on echitamine and discuss the results from the point of view of the correct structure.

In agreement with Goodson and Henry[2] the salt obtained by treatment of the alkaloid with hydrochloric acid was found to analyse for the formula $C_{22}H_{29}O_4N_2Cl$. However, potentiometric titration with N/100 alkali indicated that the salt was a quaternary chloride and not a hydrochloride. Echitamine chloride contains one OMe and one NMe. Although the infra-red spectrum in hexachlorobutadiene mull* did not show the expected band at 7·2 μ, Kuhn–Roth estimation indicated the presence of one CMe group. The chloride showed ultra-violet absorption maxima at 235 and 295 mμ (log ε 3·93, 3·55) which were unchanged even on addition of strong acid. On the basis of the findings of Hodson and Smith,[8] it can be inferred that the two nitrogen atoms in echitamine chloride are not separated by more than two carbon atoms.

* Kindly determined by Dr. N. Sheppard.

[1] G. Besanez, *Liebigs Ann.* **176**, 88 (1875); O. Hesse, *Ibid.* **176**, 326 (1875); **203**, 144 (1880); E. Harnack, *Ber. Dtsch. Chem. ges.* **13**, 1648 (1880).

[2] J. A. Goodson and T. A. Henry, *J. Chem. Soc.* **127**, 1640 (1925); J. A. Goodson, *Ibid.* 2626 (1932).

[3a] A. J. Birch, H. F. Hodson and G. F. Smith, *Proc. Chem. Soc.* 224 (1959); [b] A. J. Birch, H. F. Hodson, B. Moore, H. Potts, and G. F. Smith, *Tetrahedron Letters* No. 19, 36 (1960).

[4] H. Conroy, R. Bernasconi, P. R. Brook, R. Ikan, R. Kurtz and K. W. Robinson, *Tetrahedron Letters* No. 6, 1 (1960).

[5a] D. Chakravarthi, R. N. Chakravarthi, R. Ghose and Sir Robert Robinson, *Tetrahedron Letters* No. 10, 10 (1960); [b] *Ibid* No. 11, 25 (1960).

[6a] S. Ghosal and S. Ghosh Majumdar, *Chem. & Ind.* 19 (1960); [b] A. Chatterjee, S. Ghosal and S. Ghosh Majumdar, *Ibid* 265 (1960); [c] A. Chatterjee and S. Ghosal, *Naturwissenschaften* **47**, 234 (1960).

[7a] T. R. Govindachari and S. Rajappa, *Proc. Chem. Soc.* 134 (1959); [b] *Chem. & Ind.* 1154 (1954); [c] *Ibid* 1549 (1959).

[8] H. F. Hodson and G. F. Smith, *J. Chem. Soc.* 1877 (1957).

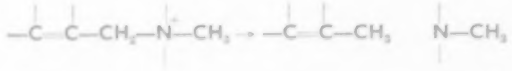
The infra-red absorption spectrum of echitamine chloride showed bands at 3·04 (OH), 3·17 (NH), 5·79 (—COOMe) and 13·2 μ (*o*-di-substituted benzene), but no band near 4·15 μ ($\overset{+}{=}$NH).

The ultra-violet absorption spectrum of the acetyl derivative of echitamine chloride (λ_{max} 235, 295 mμ log ε 3·94, 3·50) indicated clearly that N_a-acetylation had not taken place. That only O-acetylation had occurred was further supported by the infra-red absorption spectrum which showed bands at 2·92 (NH), 5·70 and 8·14 μ (OAc).

Mild alkaline hydrolysis of echitamine chloride gave demethylechitamine,[2] which was easily shown to be a betaine. In the infra-red absorption spectrum, the ester band at 5·79 μ had disappeared, and instead, the COO^- band made its appearance at 6·25 μ.

Reduction of echitamine chloride in aqueous solution at atmospheric pressure and room temperature in presence of Pd/C gave a tertiary base, m.p. 150–165°, which undoubtedly contained only three oxygen atoms. Since even carbinolamines were unlikely to undergo hydrogenolysis under the extremely mild conditions of this reduction, at an early stage of our work we suggested the possibility[7b] of echitamine chloride being actually $C_{22}H_{27}O_3N_2Cl{\cdot}H_2O$. The correct explanation was first given by Conroy *et al.*[4] who suggested that the proximate product of reduction was so constituted as to lose a molecule of methanol with formation of a lactone. The reduction product was named echitinolide by these authors and correctly formulated as $C_{21}H_{26}O_3N_2$. We came to the same conclusion independently on the basis of experimental evidence to be discussed later. To avoid confusion, we adopt the names echitinolide and isoechitinolide suggested by Conroy *et al.*

The ease of formation of the tertiary base echitinolide from echitamine chloride suggests that the latter is an allyl quaternary ammonium salt. Further, since echitinolide contains two CMe groups as shown by Kuhn–Roth estimation, the principal step in the reduction can be formulated as:



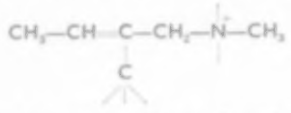
The cleavage of this bond seems to be a necessary condition for the second step, viz., the interaction of the carbomethoxy group with a hydroxyl group with expulsion of methanol and formation of a σ-lactone, since echitamine chloride itself is stable to hot hydrochloric acid.*

The ultra-violet absorption spectrum of echitinolide shows maxima at 247, 310 mμ (log ε 3·90, 3·54), typical of dihydroindole. Both these maxima undergo a hypsochromic shift of about 10 mμ in acid solution. On the basis of the work of Hodson and Smith,[8] it can be inferred that N_a and N_b are separated by a single carbon atom. Echitinolide shows infra-red absorption bands at 2·75 (OH), 2·88 (NH) and 5·80 μ (δ-lactone). Acetylation of echitinolide under vigorous conditions yielded a diacetyl derivative, m.p. 210–214°, in which N_a has been acetylated as indicated by the infra-red (amide band at 6·0 μ) and ultra-violet spectra (λ_{max} 255 mμ; log ε 4·07; λ_{infl} 282 mμ, log ε 3·53) and a positive Otto reaction. Hence echitinolide (and echitamine

* Cf. however, reference 5*a*.

chloride also) should contain a free $N_a H$ group. Mild alkaline hydrolysis of O,N-diacetylechitinolide yielded N-acetylechitinolide, m.p. 160–163° (amide band at 6·02 μ; OH band at 2·71 μ).

Independently, Birch *et al.*[3a] reported results of their work on echitamine in broad agreement with those discussed above.* They further provided conclusive evidence for the presence of an ethylidene group in echitamine chloride and echitinolide, by the isolation in good yield of acetaldehyde on ozonolysis of these compounds. In addition, they obtained α-methylbutyric acid by a modified Kuhn–Roth oxidation of dihydroechitinolide (Base C), proving the presence of the feature



in echitamine chloride. In our experiments it was found that ozonolysis of echitinolide in 2 per cent acetic acid yielded acetaldehyde, but ozonolysis in chloroform solution yielded a small amount of formaldehyde as the only isolable volatile product. Although the reason for this discrepancy is obscure, the presence of an ethylidene group in echitamine chloride can be taken as settled, since there is no indication in the infra-red or N.M.R. spectra of the presence of a vinyl group.

On warming echitinolide with dilute mineral acid, an isomer isoechitinolide, m.p. 180–182°, was formed† whose N-acetyl derivative, m.p. 172–173°, (I.R. band at 6·02 μ; no band in the OH region) was identical with the product obtained by warming N-acetylechitinolide with dilute acid. Isoechitinolide was a tertiary base analysing for the formula $C_{21}H_{26}O_3N_2$ like echitinolide. Isoechitinolide could also be obtained by the following sequence of reactions (Chart I): Demethylechitamine

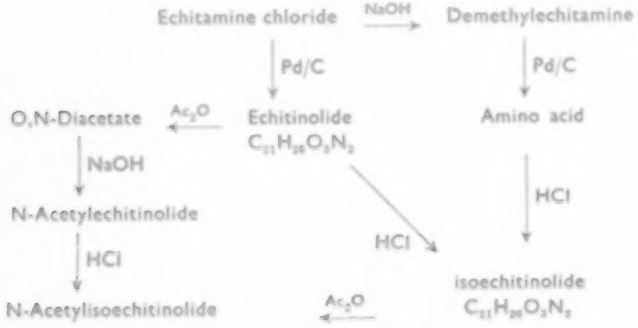


Chart I

was reduced in presence of Pd/C to yield a non-crystalline amino acid (no band in the carbonyl region below 6·3 μ) which on warming with dilute acid yielded isoechitinolide. The latter therefore cannot contain the carbomethoxy group present in echitamine chloride. Two of its oxygen atoms should be present as part of a lactone system. N-Acetylisoechitinolide has no active hydrogen and isoechitinolide can be

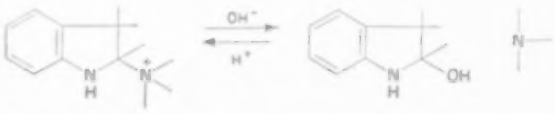
* We have not had access so far to the material in refs. 2 and 3 in the publication of Birch *et al.*[3a]

† We thank Prof. Conroy for carrying out an infra-red comparison of our samples of echitinolide and isoechitinolide with theirs. They were found to be identical, although there is a large difference in their reported m.p. for isoechitinolide and ours.

recovered unchanged after refluxing with methanolic sodium borohydride. The third oxygen atom should therefore be present as an ether function. In agreement, the infra-red spectrum of isoechitinolide does not show any absorption in the hydroxyl region, and shows a peak at 5·7 μ characteristic of a δ-lactone. Ozonolysis of isoechitinolide did not yield any volatile product unlike echitinolide, and N-acetylisoechitinolide was recovered unchanged after prolonged treatment with osmium tetroxide–sodium metaperiodate. There could be no doubt that the ethylidene group present in echitinolide had disappeared as a result of addition of some sort. These results could be rationalized only if echitinolide were itself a lactone and isoechitinolide arises from it by addition of a hydroxyl group to the ethylidene group under acid catalysis with formation of a cyclic ether. Modified Kuhn–Roth oxidation of isoechitinolide did not yield any propionic acid (paper chromatography). The N.M.R. spectrum of isoechitinolide, however, showed conclusive evidence for the formation of an ethyl group attached to a carbon bearing no hydrogen atoms, a feature not present in the N.M.R. spectrum of echitinolide. (Triplet centred at $\tau = 9{\cdot}38$, J = 7 cps; quartet centred at $\tau = 8{\cdot}69$, J = 8 cps).

Earlier we had inferred on the basis of U.V. absorption data that echitinolide contained an N_a—C—N_b system. A characteristic feature of such systems is the cleavage of the —C—N_b bond on reduction with zinc and hydrochloric acid.[8,9] Echitinolide, however, merely underwent the transformation isoechitinolide (*vide supra*) under these conditions, there being no other change.

Echitinolide yielded a methiodide under forced conditions. Treatment of an aqueous solution of this methiodide with 2 N alkali led to the immediate separation of a tertiary base, echitinolidemethine, $C_{22}H_{30}O_4N_2$, m.p. 193° (decomp). The remarkable facility with which this transformation occurred was suggestive of the presence of an eserine-like system[10] in echitinolide. Echitinolidemethine showed U.V. absorption maxima at 245, 307 mμ in ethanol, unchanged by the addition of alkali. In ethanolic hydrochloric acid the maxima were shifted to 240 and 297 mμ, suggesting the reformation of the —C—N_b bond cleaved by alkali. These transformations could be formulated as:



Echitinolidemethine was also stable to oxidation by potassium ferricyanide, suggesting that the indolinol hydroxyl group was tertiary. Although fully aware that N_a-unsubstituted 2-hydroxyindolines might be too unstable to exist, and readily change over to the corresponding indolenines, it was considered likely that in the present instance some structural feature stood in the way of such dehydration.

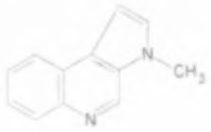
Reduction of echitinolidemethine with zinc and hydrochloric acid yielded desoxyisoechitinolidemethine, $C_{22}H_{30}O_3N_2$, m.p. 200–203°. In the formation of this compound not only had the indolinol hydroxyl group been hydrogenolysed as expected, but the addition of a hydroxyl group to the ethylidene function had also taken place.

[8] [a] E. Stedman and G. Barger, *J. Chem. Soc.* **127**, 247 (1925); [b] P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.* **57**, 539 (1935).

[10] M. Polonovski and M. Polonovski, *Bull. Soc. Chim.* **23**, 335 (1918); H. F. Hodson, G. F. Smith and J. T. Wrobel, *Chem. & Ind.* 1551 (1958).

The U.V. absorption spectrum of this compound in ethanol solution showed maxima at 247, and 307 mμ (log ε 3·97, 3·59) unchanged by the addition of acid, since the possibility of recyclization with formation of the N_a—C—N_b system no longer existed after the removal of the indolinol hydroxyl group.

In an attempt to obtain a clue to the skeletal structure present in echitamine, echitinolide was submitted to selenium dehydrogenation. The product, echitamyrine, $C_{12}H_{10}N_2$, was identified as 1′-methylpyrrolo (2′:3′-3:4)-quinoline (I), by comparison with an authentic sample obtained by silver acetate oxidation of calycanthine.[11]



I

Echitamyrine could conceivably arise either from an α- or a β-type dihydroindole alkaloid with equal facility and did not therefore prove to be of value in the formulation of structure for echitamine.

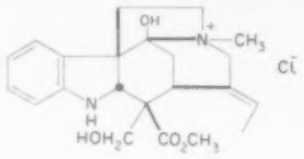
When most of the work outlined above had been concluded, Conroy *et al.* published a paper[4] in which structure II was advanced for echitamine chloride, III for echitinolide and IV for isoechitinolide. Convincing evidence for the presence of a unit in echitamine chloride was obtained by heating with potassium t-butoxide and effecting a retro-aldol reaction, the product alloechitamine being formulated as V. The arguments advanced by Conroy *et al.* appeared to be quite in keeping with the experimental evidence we had secured, except in regard to the ultra-violet absorption data, mainly on the basis of which we had suggested the presence of an N_a—C—N_b system. According to the work of Hodson and Smith[8] a compound having the structure II suggested for echitamine chloride would be expected to show indoline absorption in neutral solution and benzenoid absorption in acid solution. In fact compounds of closely related structure such as hemitoxiferine-I[12] and tetrahydrofluorocurarine[13] do exhibit this behaviour. According to Conroy *et al.* the failure to protonate even in strongly acid solution was due to steric hindrance in the neighbourhood of N_a in their structure II. The hypsochromic shift observed in the case of echitinolide and isoechitinolide in acid solution was supposedly due to a change in conformation of the N_a—C_2 bond from axial to equatorial.

The structure proposed by Sir Robert Robinson *et al.*[5] for echitamine chloride differs only in minor detail (about the placement of one of the hydroxyl groups) from that of Conroy *et al.* The structure put forward by Chatterjee *et al.*[6] is clearly untenable since echitamine chloride has undoubtedly a free N_aH group.

In their later publication[3b] Birch *et al.*, while conceding that the structure II advanced by Conroy 'goes a long way towards interpreting the known reactions of the alkaloid' have drawn attention to a number of facts which make this structure less

[11] E. Späth, W. Stroh, E. Lederer and K. Eiter, *Monatsh.* **79**, 11 (1948); K. Eiter, *Ibid.* **79**, 17 (1948); K. Eiter and M. Nagy, *Ibid.* **80**, 607 (1949).
[12] A. R. Battersby and H. F. Hodson, *Proc. Chem. Soc.* 287 (1958).
[13] W. von Philipsborn, K. Bernauer, H. Schmid and P. Karrer, *Helv. Chim. Acta* **42**, 461 (1959).

acceptable. The most pertinent objection in our view is the following: O,O-diacetyl-echitamine chloride was hydrogenated (Emde) to a di-O-acetyl base, in which there is no possibility of any conformational transformation of the type suggested by Conroy *et al.* Still, it shows the hypsochromic shift of 10 mμ of both maxima in acid solution,



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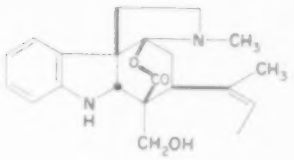

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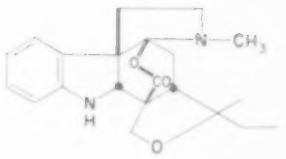

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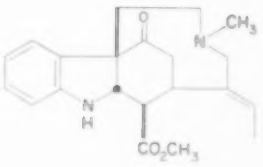


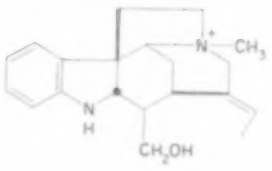
V

associated with the presence of an N_a—C—N_b system. Birch *et al.* have concluded that the most acceptable structure for echitamine chloride would be one in which this system was present.

Subsequent to the publication by Conroy *et al.*, we also carried out certain experiments whose results cannot be satisfactorily explained on the basis of the structures ascribed by these authors to echitinolide and isoechitinolide. Conceding that the presence of an electron-withdrawing carbomethoxy group in the neighbourhood of N_a might prevent protonation of N_a, we reduced echitinolide with lithium aluminium hydride to a non-crystalline alcohol (No I.R. band in the carbonyl region). The reduction product showed indoline absorption in neutral solution, and only the usual hypsochromic shift even in 5N acid solution, but not benzenoid absorption. Similarly isoechitinolide was reduced to a diol which was characterized by the formation of a

crystalline O,O,N-tribenzoate, m.p. 214° (I.R. bands at 5·83, 6·15 μ; no band in the 2·5–3 μ region). On the basis of Conroy's structure for isoechitinolide one would have expected only a O,N-dibenzoate, since the carbinolamine hydroxyl would surely have hydrogenolysed under the conditions of reduction.

In a further attempt to obtain evidence for the correctness of structure II proposed for echitamine chloride, alloechitamine[4] was reduced with lithium aluminium hydride and the non-crystalline alcohol formed was heated with 4 N hydrochloric acid leading to a minute amount of a crystalline quaternary chloride. The last compound should have structure VI on the basis of structure II for echitamine chloride. Two compounds corresponding to this gross structure VI are known, one derived from Wieland–Gumlich aldehyde,[14] the other being tetrahydrofluorocurarin.[13] Comparison of our



VI

compound with the latter showed that there were distinct differences between the two in their infra-red spectra, colour reactions and behaviour in paper chromatography.*

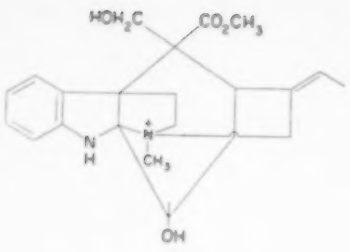
The deadlock about the structure of echitamine has been resolved by the brilliant elucidation of structure of echitamine bromide by the X-ray crystallographic method effected by Prof. Monteath Robertson *et al.*,[15] according to which echitamine bromide should be formulated as VII, containing the N_a—C—N_b system suggested by us and by Birch *et al.*, on the basis of ultra-violet absorption characteristics. Independent confirmation of this structure has been obtained by Dr. S. Ramaseshan[16] working on anhydrous crystals of echitamine iodide and chloride, also by the X-ray method. On the basis of this structure, echitinolide, isoichitinolide and alloechitamine can be formulated as VIII, IX and X respectively. The transannular interaction between a carbonyl group and N_b observed by Conroy *et al.*, is equally feasible with the new correct formulation of alloechitamine. It is indeed a matter for surprise that two structures like II and VII for echitamine chloride which are so utterly dissimilar should be able to account for most of the experimental results with equal facility.

The structure VII now established for echitamine chloride could conceivably arise from an intermediate of the type XI derivable from a normal yohimbine type precursor by Woodward fission of ring E and cleavage of the C_3—N_b bond. Oxidative coupling of C_{16} with C_7 of this intermediate in the indolenine form and formation of a N_b—C_2 bond would lead to structure VII. The hydroxyl group at C_3 is at a position compatible with this scheme.

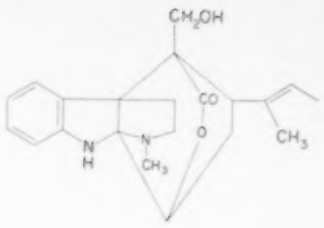
On the basis of structure VII for echitamine chloride, desoxyisoechitinolide methine should be formulated as XII. This compound exhibits indoline absorption

* We are extremely grateful to Prof. P. Karrer who carried out this comparison.

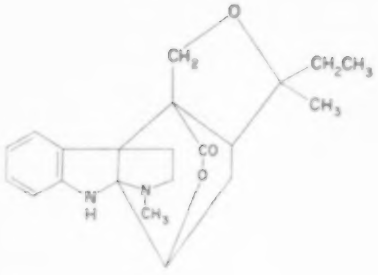
[14] K. Bernauer, F. Berlage, W. v. Philipsborn, H. Schmid and P. Karrer, *Helv. Chim. Acta* **41**,2 293 (1958).
[15] J. A. Hamilton, T. A. Hamor, J. Monteath Robertson and G. A. Sim, *Proc. Chem. Soc.* 63 (1961).
[16] H. Manohar and S. Ramaseshan, *Curr. Sci., India* **30**, 5 (1961). We are deeply indebted to Prof. Robertson and Dr. Ramaseshan for communicating their results to us in advance of publication.



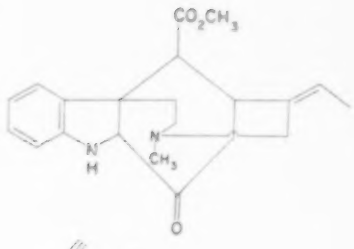
VII



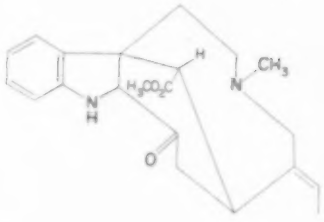
VIII



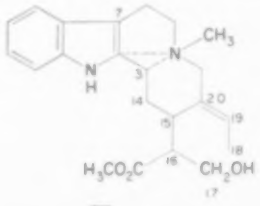
IX



X



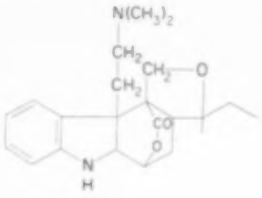
even in 0·1 N acid solution, instead of benzenoid absorption as expected. Alloechitamine, now formulated as X exhibits indoline absorption in 0·1 N hydrochloric acid, but benzenoid absorptions in 5 N acid. In both these compounds N_b is separated by more than three carbon atoms from N_a and the spectral behaviour should be ascribed to the proximity of the carbonyl function in these compounds to N_a. The situation is analogous to that in compound XIII which shows indoline absorption in 0·2 N hydrochloric acid, and benzenoid absorption only in 2·5 N acid.[17]



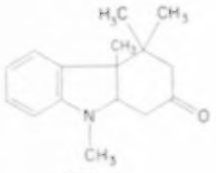
XI

[17] B. Robinson and G. F. Smith, *J. Chem. Soc.* 4574 (1960).

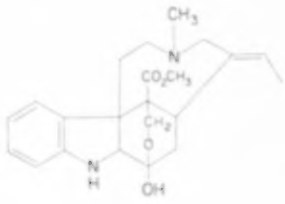
Echitamine base was obtained as a crystalline benzene solvate Conroy *et al.*[4] On the basis of the new formula for echitamine chloride, the base can be ascribed structure XIV in keeping with the properties ascribed to it by these authors.



XII



XIII



XIV

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured with a Beckmann Model DU Spectrophotometer. Unless otherwise stated, infra-red spectra were measured by Mr. S. Selvavinayakam using a Perkin–Elmer Infracord Spectrophotometer.

Isolation of echitamine

The alkaloid was isolated as its chloride according to the method described by Goodson and Henry.[5] λ_{max} in ethanol 235, 295 mμ (log ε 3·93, 3·55) (Found: C, 62·7; H, 6·9; OMe, 7·55; CMe 2·13; NMe, 4·49. $C_{22}H_{29}O_4N_2Cl$ requires: C, 62·8; H, 6·9; one OMe, 7·4; one CMe, 3·6; one NMe, 6·9%).

Echitinolide

Echitamine chloride (2 g) in water (50 ml) was shaken with hydrogen in the presence of Pd/C (5%; 2 g) at 15 lbs/in^2 for 6 hr. The solution was then filtered, basified with ammonia and extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent distilled off leaving the tertiary base as a froth (1·3 g). Crystallization from benzene–light petroleum gave *echitinolide*, m.p. 150–165°; λ_{max} in ethanol, 247, 310 mμ (log ε 3·90, 3·54); λ_{max} in ethanolic hydrochloric acid, 237, 295 mμ (log ε 3·85, 3·47). (Found: C, 71·1; H, 7·6; OMe, nil; act. H, 0·57. $C_{21}H_{26}O_3N_2$ requires: C, 71·2; H, 7·3; 2 act. H, 0·56%).

Ozonolysis of echitinolide

Echitinolide (0·5 g) in 2% acetic acid (30 ml) was ozonized at 0° (1 hr). The excess ozone was then driven off in a current of nitrogen (1/2 hr), while the solution was still cooled in ice. The acetic acid solution was then taken out and steam-distilled, the distillate being collected in a flask cooled in ice. The distillate (50 ml) was treated with alcohol (25 ml) and 2,4-dinitrophenylhydrazine (100 mg), refluxed for 3 hr, and left overnight at 30°. The crystalline derivative that had separated was collected, washed with alcohol, dried and chromatographed in benzene solution over alumina. The eluate was evaporated and the residue crystallized from alcohol to give acetaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 166–167°.

In another experiment, the ozonolysis was performed in chloroform solution, and the volatile aldehyde after decomposition of the ozonide with zinc dust, collected in a solution of dimedone. Formaldehyde dimethone (10 mg from 0·45 g echitinolide), m.p. and mixed m.p. 191°, was obtained.

O,N-*Diacetylechitinolide*

Echitinolide (0·5 g) was refluxed with pyridine (a few drops) and acetic anhydride (15 ml) for 12 hr. It was then cooled and poured on crushed ice. The solution was basified with ammonia and ether extracted. The dried (Na_2SO_4) ethereal extract was evaporated and left in vacuum to remove pyridine. Crystallization of the residue from methanol gave colourless crystals (300 mg) of the O,N-*diacetyl derivative*, m.p. 210–214°. λ_{max} 255 mμ (log ε 4·07); λ_{infl} 282 mμ (log ε 3·53). (Found: C, 68·7; H, 7·0. $C_{25}H_{30}O_5N_2$ requires: C, 68·5; H, 6·8%).

N-*Acetylechitinolide*

The above diacetate (0·5 g) in methanol (12 ml) was refluxed with potassium hydroxide (1 g) in water (5 ml) for 2½ hr. The methanol was then removed *in vacuo*, water was added and the material which had separated was extracted in ether. The ether extract was dried and the solvent distilled off. Crystallization of the residue from dry ether gave N-*acetylechitinolide*, m.p. 160–163°. (Found: C, 69·4; H, 7·1. $C_{23}H_{28}O_4N_2$ requires: C, 69·7; H, 7·1%).

Selenium dehydrogenation of echitinolide

Echitinolide (1·2 g) was intimately ground with black selenium (2 g). The dehydrogenation was carried out in two batches as follows: The mixture was introduced into a metal-bath at 250°, and the temp raised slowly to 340° (5 min), at which stage hydrogen selenide started evolving. The temp of the bath was maintained at 330–340° for 10 min. It was then cooled, the solid mass, along with the container, crushed in a mortar and mixed with alumina. Two such batches were combined and soxhleted with methanol for 10 hr. The methanol extract was filtered and the solvent distilled off. The residue, in ether, was repeatedly extracted with N HCl till the aqueous layer was no more coloured. The aqueous layer was once extracted with ether. The combined ether extracts were washed thoroughly with water and worked up for non-basic material.

The basic fraction: The aqueous acidic layer was well-cooled and basified with conc NaOH solution. The solution was ether extracted, dried (K_2CO_3) and distilled. The residue was sublimed at 180°/0·04 mm, and the sublimate resublimed. The sublimate was then taken in alcohol (3 ml) and picric acid (50 mg) added. The solution was boiled and decanted. The residual picrate was repeatedly digested with small quantities of hot alcohol and decanted to remove the green colour. At this stage, the yield of greenish-yellow picrate was 19 mg. The traces of green colour could only be removed as follows: The picrate was decomposed with sodium hydroxide solution and the base extracted in ether. The ether layer was washed twice with water, dried (Na_2SO_4), distilled and the residue sublimed at 180°/0·04 mm. The sublimate was reconverted to the picrate. Recrystallization from alcohol gave *echitamyrine picrate*, m.p. 252° (decomp) with blackening and shrinking from 242°. The m.p. was unchanged on admixture with authentic 1′-methylpyrrolo(2′,3′-3,4)quinoline picrate obtained from calycanthine. (Found: C, 53·4; H, 3·8. $C_{18}H_{13}O_7N_5$ requires: C, 52·6; H, 3·2%.)

Echitamyrine base itself was obtained by liberation from the picrate, followed by sublimation. λ_{max} in ethanol 245, 307 mμ (log ε 4·45, 3·97); λ_{max} in ethanolic HCl 245, 327, 355 mμ (log ε 4·29, 3·90, 3·95). The I.R. spectrum of the base (in $CHCl_3$) was superposable on that of 1′-methylpyrrolo-(2′,3′-3,4)quinoline.

The non-basic fraction: Careful fractional sublimation of the non-basic fraction gave only indolic material. No trace of carbazole could be detected (U.V. and colour reactions).

Attempted Zn/HCl *reduction of echitinolide*

Echitinolide (250 mg) in 5 N HCl (30 ml) was treated with zinc granules (10 g) in portions at 100° over 2 hr. The aqueous solution was decanted, cooled, diluted with water, and basified with ammonia. The product was extracted in ether, dried, and after removal of the solvent, crystallized from benzene–light petroleum to give *isoechitinolide* (see below) (200 mg), m.p. and mixed m.p. 182°.

Isoechitinolide

(a) Echitinolide (100 mg) in methanol (10 ml) was saturated with dry HCl at 0° and left at 30° for 18 hr. The solution was then evaporated to dryness *in vacuo*, the residue dissolved in water, basified with ammonia, and repeatedly extracted with ether. The ether extract was dried, and distilled. The residual solid (50 mg) was crystallized twice from benzene–pet ether to give *isochitinolide*, m.p. 180–182° (Conroy *et al.*, report m.p. 149–154°; Birch *et al.*, report m.p. 182–184°). λ_{max} in ethanol 247, 307 mμ (log ε 3·94, 3·57); λ_{max} in ethanolic HCl 237, 295 mμ (log ε 3·89, 3·48). (Found: C, 71·1; H, 7·0; OMe, nil. $C_{21}H_{24}O_3N_2$ requires: C, 71·2; H, 7·3%).

In the qualitative chromic acid oxidation method of Karrer, thic compound gave only acetic acid. No trace of propionic acid could be found.

(b) Echitinolide (1 g) was heated at 100° with 5 N HCl (20 ml) for 1½ hr. Dilution with water, basification with ammonia, ether extraction and crystallization from benzene–pet ether gave *isoechitinolide* (0·8 g) m.p. 180–182°.

Isoechitinolide from demethylechitamine

Demethylechitamine (0·6 g) in 50% aqueous alcohol (40 ml) was shaken with hydrogen at 15 lbs/in² in presence of Pd/C (5%; 0·6 g) for 6 hr. The solution was then filtered and evaporated to dryness *in vacuo*. The residual amino acid showed no carbonyl absorption band in the 5–6 μ region. The COO^- band occurred at 6·3 μ. This solid was dissolved in 5 N HCl (20 ml) and heated on a steam-bath for 1½ hr, diluted, and basified with ammonia. The product was extracted in ether, dried (K_2CO_3) and the solvent removed. The residue (0·4 g) was passed in benzene solution through a short column of acid-washed alumina. The product crystallized from benzene–pet ether as white clusters of needles, m.p. 179–182°, undepressed by admixture with isoechitinolide. The I.R. spectra of the two samples were identical.

N-*Acetylisoechitinolide*

(a) Isoechitinolide (0·3 g) was refluxed with pyridine (a few drops) and acetic anhydride (12 ml) for 8 hr. The cooled mixture was poured on crushed ice, basified with ammonia and extracted with ether. After removal of the solvent, the residue was crystallized from ether–petroleum ether to give N-*acetylisoechitinolide* (0·25 g), m.p. 172–173°. (Found: C, 69·7; H, 7·1. $C_{23}H_{26}O_4N_2$ requires: C, 69·7; H, 7·1%).

(b) N-Acetylechitinolide (75 mg) in 5 N HCl (10 ml) was heated on a steam-bath for 1 hr. The solution was cooled, diluted to 25 ml, basified with ammonia and ether extracted. The ether solution was dried (K_2CO_3), evaporated, and the residue crystallized from dry ether to give N-acetylisoechitinolide (50 mg), m.p. and mixed m.p. with the above sample, 172°.

Ozonolysis of isoechitinolide

Isoechitinolide (0·5 g) in chloroform (15 ml) was subjected to ozonolysis (1 hr). The solvent was then evaporated *in vacuo*, the residue heated in water with zinc dust at 100° (5 hr), and then steam-distilled. The distillate gave no precipitate with aqueous dimedone solution.

Action of osmium tetroxide–sodium metaperiodate on N-*acetylisoechitinolide*

N-Acetylisoechitinolide (0·25 g) in ether (30 ml) and water (25 ml) was treated with osmium tetroxide (50 mg). Sodium periodate (0·25 g) was then added to the mixture in portions with vigorous shaking during the course of 1 hr. The mixture was left overnight. The ether layer was separated, dried (Na_2SO_4) and the solvent removed by distillation. The residue on two crystallizations from ether–petroleum ether gave the original material (75 mg), m.p. and mixed m.p. 172°.

Echitinolidemethine

Echitinolide (0·6 g) was refluxed with methyl iodide (3 ml) in chloroform (5 ml) for 10 hr. The chloroform was then removed and the residue dissolved in water (5 ml). The aqueous solution was added with stirring to 2 N NaOH (12 ml). An oil separated almost immediately, and after digestion for 15 min, was extracted with ether. The ether solution was dried (Na_2SO_4) and the solvent distilled off. The residue, on crystallization from benzene–pet ether, gave *echitinolidemethine* (0·3 g), m.p. 193° (decomp). (Birch *et al.*,[20] report m.p. 169–173°) λ_{max} in ethanol 245, 307 mμ (log ε 3·92, 3·52)

unaffected by addition of alkali; λ_{max} in ethanolic hydrochloric acid 240, 297 mμ (log ε 3·88, 3·47). (Found: C, 68·9; H, 7·9. $C_{22}H_{30}O_4N_2$ requires: C, 68·4; H, 7·8%).

Desoxyisoechitinolidemethine

The above methine (100 mg) in 5 N HCl (15 ml) was treated with zinc granules (5 g) in portions at 100° over 2 hr, such that a steady rate of evolution of hydrogen was maintained. The solution was then decanted from the zinc, diluted, basified with ammonia and ether extracted. After removal of the ether, the residue was crystallized twice from benzene–pet ether to give *desoxyisoechitinolidemethine* (50 mg), m.p. 200–203°. λ_{max} in ethanol 247, 307 mμ (log ε 3·97, 3·59) unchanged on addition of acid. (Found: C, 71·6; H, 8·2. $C_{22}H_{30}O_3N_2$ requires: C, 71·4; H, 8·1%).

Attempted ferricyanide oxidation of echitinolidemethine

The methine (0·9 g) in alcohol (2 ml) was added to potassium ferricyanide (2·4 g) in water (33 ml) containing sodium hydroxide (0·8 g). The solution was refluxed for 5 min, cooled and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and after removal of the solvent, the residue passed through a column of acid-washed alumina in benzene solution. Evaporation of the eluate, and crystallization of the residue (0·5 g) from benzene–pet ether gave back the methine, m.p. and mixed m.p. 193° (decomp).

Lithium aluminium hydride reduction of echitinolide

Echitinolide (0·5 g) in dry tetrahydrofuran (5 ml) was added to a suspension of lithium aluminium hydride (1 g) in dry ether (40 ml). The mixture was stirred for 5 hr, left overnight and worked up as usual. The product (0·5 g) was amorphous and could not be crystallized. λ_{max} in ethanol 250, 307 mμ (log ε 3·84, 3·41); λ_{max} in 0·1 N or 5 N HCl, 240, 295 mμ (log ε 3·82, 3·39). It had no band in the carbonyl region of the infra-red spectrum. Benzoylation or acetylation of the compound led to no crystalline material.

Lithium aluminium hydride reduction of isoechitinolide

Isoechitinolide (0·2 g) in tetrahydrofuran (10 ml) was added to lithium aluminium hydride (0·5 g) in dry ether (40 ml). The mixture was stirred for 3 hr, left overnight, and worked up as usual. The product was a froth, having no carbonyl band in the infra-red. The product (0·2 g) in pyridine (5 ml) was treated with benzoyl chloride (2 ml) and left for 3 days at 30°. It was then poured into water (50 ml), extracted in benzene, and the benzene layer washed with 2N Na_2CO_3 solution. After removal of benzene and pyridine *in vacuo*, the residue was chromatographed in benzene over alumina. Crystallization from methanol gave the *benzoate*, m.p. 214°. (Found: C, 75·2, 75·3; H, 6·6, 6·4. $C_{42}H_{42}O_6N_2$ requires: C, 75·2; H, 6·3%).

Lithium aluminium hydride reduction of alloechitamine

Alloechitamine (0·12 g) in dry ether (20 ml) was added to lithium aluminium hydride (0·25 g) in dry ether. The product was non-crystalline. The product was heated on a water-bath with 4 N HCl (10 ml) for 3 hr, evaporated to dryness *in vacuo*, and the residue crystallized from methanol to give a product (ca. 1 mg), λ_{max} in ethanol 245, 295 mμ (log ε 3·83, 3·43).

Acknowledgements—Our grateful thanks are due to Dr. George Slomp, Upjohn Co. for the measurement and interpretation of the N.M.R. spectra of echitamine and its numerous derivatives. We are indebted to Prof. Richard Kuhn and Mr. S. Selvavinayakam for the microanalyses. This work was carried out during the tenure of a C.S.I.R. Senior Research Fellowship held by one of us (S. R.).

Tetrahedron, 1961, Vol. 15, pp. 144 to 153. Pergamon Press Ltd. Printed in Northern Ireland

ELIMINATION OF THE 4-HYDROXYL GROUP OF THE ALKALOIDS RELATED TO MORPHINE—I

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(*Received* 13 *March* 1961)

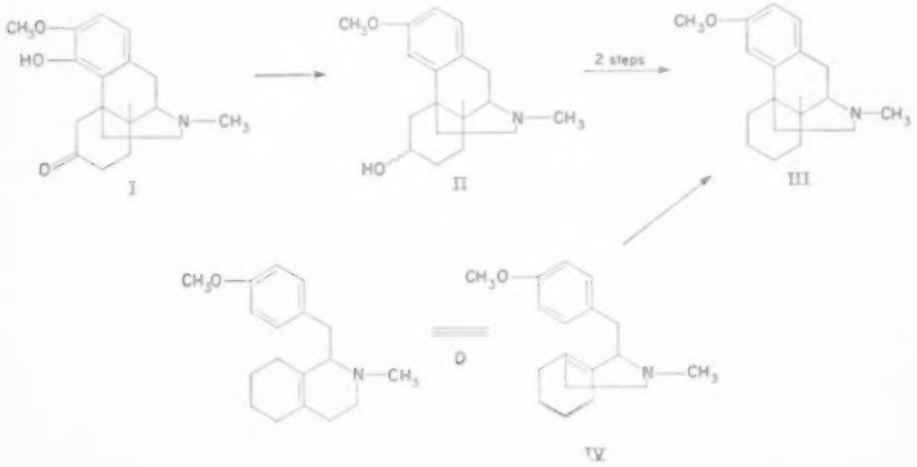
Abstract—Sinomenine, an alkaloid of the Japanese plant *Sinomenium acutum*, was converted to the 4-phenylether by the Ullmann reaction in a good yield. The Clemmensen reduction of sinomenine-phenylether and of its derivatives gave (+)-3-methoxy-4-phenoxy-N-methyl-Δ^{x}-morphinan.

Hydrogenation and successive sodium–liquid ammonia reduction of (+)-3-methoxy-4-phenoxy-N-methyl-Δ^{x}-morphinan gave (+)-3-methoxy-N-methylmorphinan.

IN 1921, Speyer *et al.*[1] reported that the 4-hydroxyl group of dihydrothebainone (I) was eliminated by the Tafel reduction to yield dihydrothebacodine (II) and that desoxydihydrothebacodine (III), m.p. 146° was obtained from this compound.

In 1932, however, Small *et al.*[2] stated that they were unable to obtain dihydrothebacodine (II) by the reaction according to the method of Speyer *et al.*

In 1949, Grewe *et al.*[3] synthesized 3-methoxy-N-methylmorphinan (III) from 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (IV) by ring-closure. Later, Schnider *et al.*[4] improved the method for preparing these octahydroisoquinoline derivatives and obtained many other morphinan derivatives.

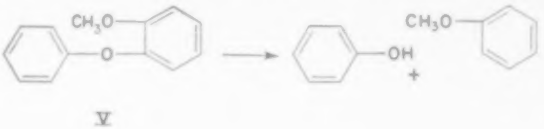


An outline of this paper was reported at the I.U.P.A.C. Symposium on the Chemistry of Natural Products in Melbourne, Australia, August (1960).

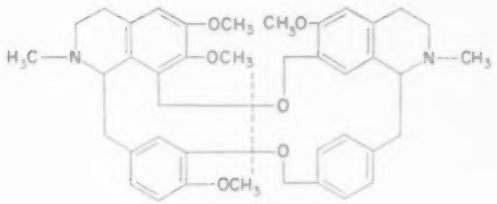
[1] E. Speyer and S. Siebert, *Ber. Dtsch. Chem. Ges.* **54**, 1519 (1921).
[2] L. F. Small and F. L. Cohen, *J. Amer. Chem. Soc.* **54**, 802 (1932).
[3] R. Grewe, A. Mondon and E. Nolte, *Liebigs Ann.* **564**, 161 (1949).
[4] O. Schnider and A. Grüssner, *Helv. Chim. Acta* **32**, 821 (1949); O. Schnider and A. Grüssner, *Ibid.* **34**, 2211 (1951); O. Schnider, A. Brossi and K. Vogler, *Ibid.* **37**, 710 (1954).

They reported that (−)-3-methoxy-N-methylmorphinan (III) does not melt at 146°, but at 109–111°. As a result of their work, it has been certified that desoxydihydrothebacodine obtained by Speyer *et al.* is not (−)-3-methoxy-N-methyl-morphinan. And since then no one has succeeded in eliminating the 4-hydroxyl group of the alkaloids related to morphine.

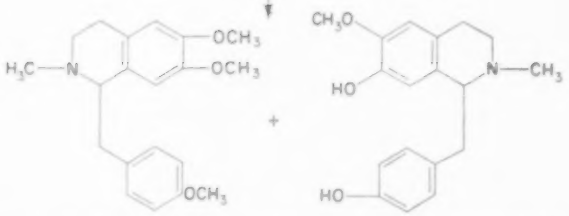
Sowa[5] succeeded in cleaving 2-methoxydiphenylether (V) into anisol and phenol by treating it with sodium in liquid ammonia and Tomita[6] applied this reaction to some alkaloids of the biscoclaurine group and obtained two kinds of coclaurine



V



Isotetrandrine



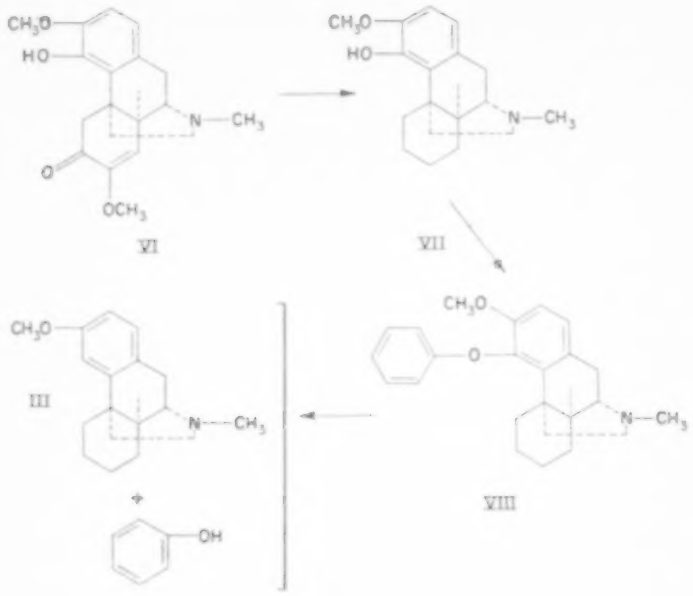
derivatives. These compounds all have the methoxyl group in the *ortho*-position of the ethereal oxygen linkage and no substituent in the *para*-position of same.

Sinomenine is an alkaloid isolated from the roots of *Sinomenium acutum* Rehed *et* Wils by Ishiwari[7] in 1920 and its structure was determined as VI by Kondo and Ochiai[8] and also by Goto.[9]

Desmethoxydesoxodihydrosinomenine i.e. (+)-tetrahydrodesoxycodeine (VII) was prepared from sinomenine (VI) by the Clemmensen reduction. We carried out the Ullmann reaction on this compound (VII) with bromobenzene in a pyridine solution in the presence of finely powdered potassium carbonate and copper and its 4-phenylether (VIII) was obtained in about 50 per cent yield.

[5] P. A. Sartovetto and F. J. Sowa, *J. Amer. Chem. Soc.* **59**, 603 (1937); A. L. Kranzfelder and F. J. Sowa, *Ibid.* **59**, 1488 (1937); F. C. Weber and F. J. Sowa, *Ibid* **60**, 94 (1938).
[6] M. Tomita, E. Fujita and F. Murai, *Yakugaku Zasshi* **71**, 226 (1951); M. Tomita, Y. Inubushi and H. Niwa, *Ibid.* **72**, 206 (1952).
[7] N. Ishiwari, *Chugai Iji Shimpo* **959**, 1 (1920).
[8] H. Kondo and E. Ochiai, Yakugaku Zasshi, No. 549, 913 (1927).
[9] K. Goto and H. Sudzuki, *Bull. Chem. Soc. Japan* **4**, 163 (1929).

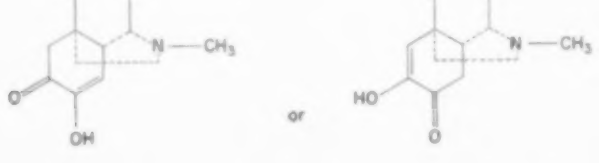
Treatment of this compound (VIII) with metallic sodium in liquid ammonia at −55°–−60° gave (+)-3-methoxy-N-methylmorphinan (III) in about 95 per cent yield together with phenol as expected. This compound melted at 109–111° and was not depressed on admixture with an authentic sample obtained by the method of Schnider.



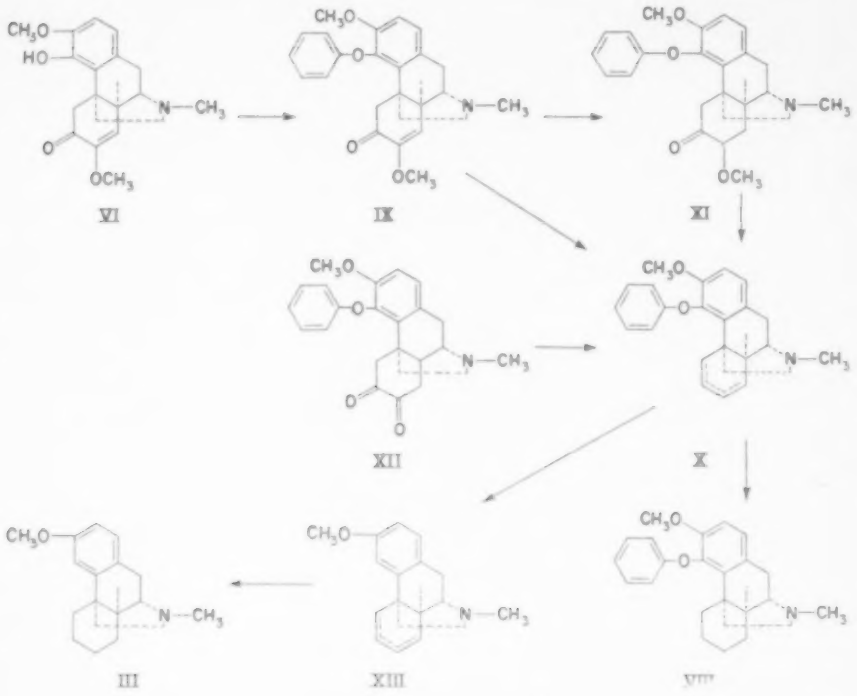
In order to expand the application of this reaction, sinomenine was analogously treated with bromobenzene by the Ullmann reaction to yield its 4-phenylether (IX) in about 85 per cent yield. When the Clemmensen reduction of this compound was carried out, the 6-carbonyl and the 7-enolmethylether groups were eliminated simultaneously and (+)-3-*methoxy*-4-*phenoxy*-*N*-methyl-Δ^x-morphinan (X) was obtained in about 90 per cent yield. However, the location of this double bond in ring C has not yet been determined. This compound (X) was also obtained from dihydrosinomenine-4-phenylether (XI) and sinomeninone-4-phenylether* (XII) by the Clemmensen reduction.

Hydrogenation of the unsaturated compound (X) over Adams' platineoxide afforded (+)-3-methoxy-4-phenoxy-N-methylmorphinan (VIII) in an excellent yield and sodium-liquid-ammonia reduction of X gave (+)-3-methoxy-N-methyl-Δ^x-morphinan (XIII) in about 90 per cent yield. This desoxy base XIII was also hydrogenated to (+)-3-methoxy-N-methylmorphinan (III) in a very good yield.

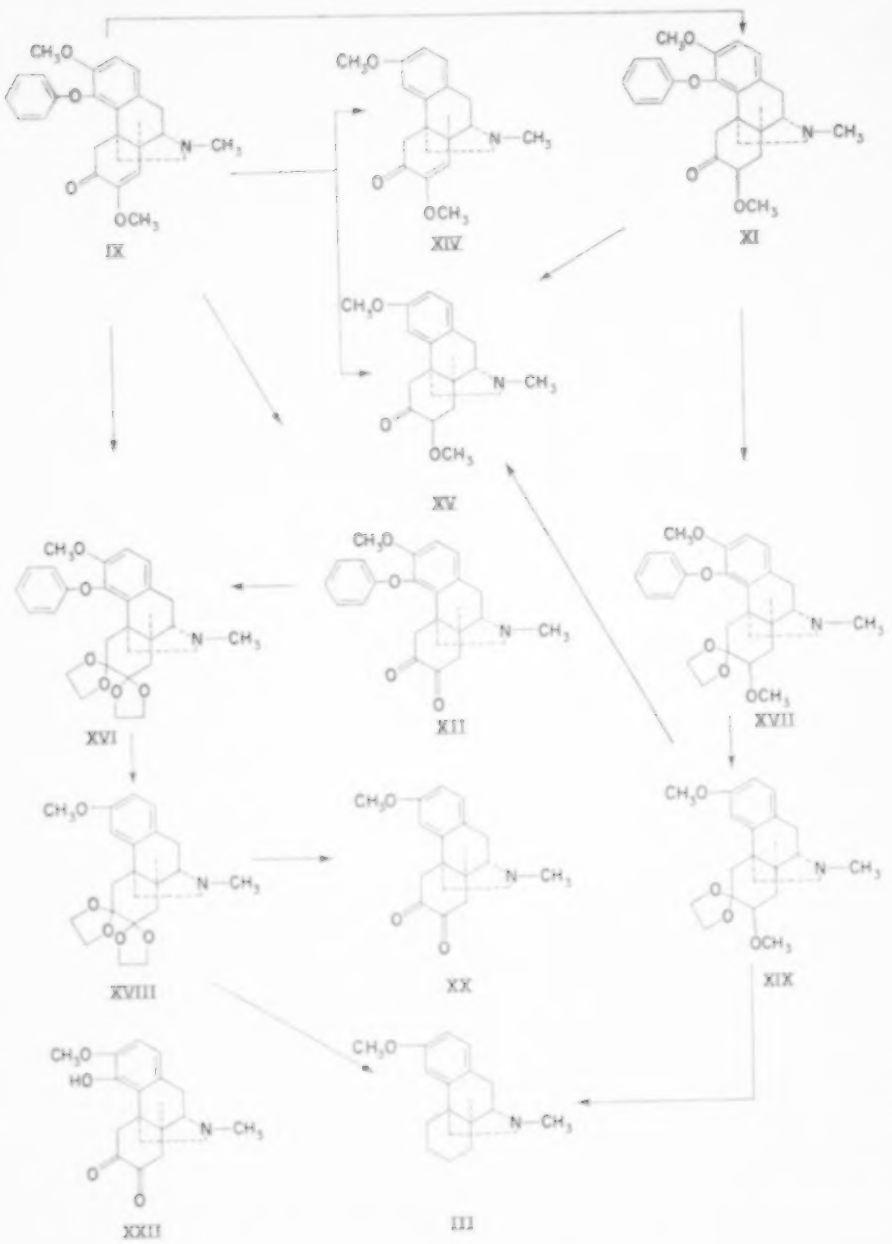
* We allot the diketon system to this compound tentatively because this compound may be:



For the preparation of 4-desoxy compounds containing substituents in ring C, sinomenine-4-phenylether (IX) was treated with sodium in liquid ammonia and desoxysinomenine (XIV) and desoxydihydrosinomenine (XV) were obtained. The latter was also obtained from dihydrosinomenine-4-phenylether (XI) in an excellent



yield by the similar reduction. Treatment of sinomenine-4-phenylether (IX) with ethylene glycol and *p*-toluene-sulphonic acid gave the 6,7-diethylene glycol ketal (XVI) of sinomeninone-4-phenylether in about 65 per cent yield. The infra-red spectrum of this compound showed no absorption band due to the enol methylether and the carbonyl groups. Furthermore, the structure of this compound was confirmed on admixture with the sample obtained from sinomeninone-4-phenylether (XII). Dihydrosinomenine-4-phenylether (XI) was also converted to the 6-ethylene glycol ketal derivative (XVII) in a very good yield. These ketal derivatives XVI and XVII were treated with sodium in liquid ammonia to yield the ketal derivatives of the 4-desoxy compounds XVIII and XIX respectively. Treatment of the ketal derivatives XVIII and XIX with dilute hydrochloric acid afforded the corresponding carbonyl compounds XX and XV. The infra-red spectrum of desoxysinomeninone (XX) showed an absorption band due to α,β-unsaturated ketone as in the case of sinomeninone (XXII). The Clemmensen reduction of the 6-ethylene glycol ketal (XIX) of desoxydihydrosinomenine and the 6,7-diethylene glycol ketal (XVIII) of desoxysinomeninone did not afford the unsaturated compound, but (+)-3-methoxy-N-methyl-morphinan (III) contrary to the case of the 4-phenylethers of the sinomenine derivatives.


IX
XIV
XI
XV
XVI
XII
XVII
XVIII
XX
XIX
XXII
III

EXPERIMENTAL

All melting points are uncorrected. Analyses of the compounds were carried out by Messrs. K Miyahara, Y. Daikatsu, T. Takaoka and Miss U. Kasugai. The infra-red spectra were determined by Messrs. Y. Matsui and M. Takasuka on a Koken D.S. 301 infra-red spectrophotometer.

Sinomenine-4-phenylether (IX)

A solution of 16·5 g sinomenine in 50 cc freshly distilled dry pyridine was refluxed with 15·7 g bromobenzene, 10·3 g finely powdered K_2CO_3 and 0·5 g copper for 15 hr. The mixture was filtered while hot and washed with hot pyridine. The solvent was removed by distillation and the residue in benzene, filtered, washed 3 times with water and dried over K_2CO_3. The benzene solution was chromatographed on alumina and the benzene eluate gave 22 g of the crude base. Recrystallization from benzene gave 20·7 g of the pure benzene adduct. (85%), m.p. 122–124°. $[\alpha]_D^{19}$ −111·9° ± 2° (*c*, 0·940, alc.). (Found: C, 76·92; H, 7·09; N, 2·76. $C_{25}H_{27}O_4N{\cdot}C_6H_6$ requires: C, 76·99; H, 6·88; N, 2·90%).

The pyridine adduct separated on cooling the reaction mixture and crystallizing from pyridine, m.p. 120–123°, $[\alpha]_D^{19}$ −116·4° ± 2° (*c*, 0·975, alc.). (Found: C, 74·51; H, 6·67; N, 5·78. $C_{25}H_{27}O_4N{\cdot}C_5H_5N$ requires: C, 74·35; H, 6·66; N, 5·78%).

The free base was crystallized from ether, m.p. 142–143°, $[\alpha]_D^{18}$ −137·8° ± 2° (*c*, 0·994, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1690 cm^{-1} (conjugated C=O): 1632 cm^{-1} (enol methylether.) (Found: C, 73·94; H, 7·07; N, 3·27. $C_{25}H_{27}O_4N$ requires: C, 74·05; H, 6·75; N, 3·45%).

The picrate was prepared in ether and crystallized from alcohol, m.p. 230–231°. (Found: C, 58·95; H, 4·93; N, 8·83. $C_{25}H_{27}O_4N{\cdot}C_6H_3O_7N_3$ requires: C, 58·67; H, 4·77; N, 8·83%).

The methiodide was prepared in and crystallized from alcohol, m.p. 206° (dec), $[\alpha]_D^{19}$ −121·5° ± 2° (*c*, 0·969, alc.). (Found: C, 56·46; H, 6·04; N, 24·2; I, 21·31. $C_{25}H_{27}O_4N$. CH_3I requires: C, 56·66; H, 6·11; N, 2·36; I, 21·39%).

Dihydrosinomenine-4-phenylether (XI)

A solution of 12 g of the benzene adduct of sinomenine-4-phenylether in 100 cc alcohol was hydrogenated over 100 mg Adams' catalyst at room temp. After absorption of 700 cc hydrogen, the solution was filtered and evaporated to dryness. The residue in a small amount of alcohol was treated with an alcoholic solution of picric acid. The yield of yellow crystalline picrate m.p. 208° (dec.), was almost quantitative. (Found: C, 58·02; H, 5·27; N, 8·32. $C_{25}H_{29}O_4N{\cdot}C_6H_3O_7N_3$ requires: C, 58·84; H, 5·07; N, 8·80%).

A sample of the picrate was converted to the free base by partition between ether and dil NaOH. The ether extracts were washed with dil NaOH and water, dried, filtered and chromatographed on alumina, yielding a colorless oil which crystallized on standing. Crystallization from ether gave pure dihydrosinomenine-4-phenylether, m.p. 149–154°, $[\alpha]_D^{24}$ −5·9° ± 2° (*c*, 0·904, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1730 cm^{-1} (unconjugated >C=O). (Found: C, 73·84; H, 7·25; N, 3·41. $C_{25}H_{29}O_4N$ requires: C, 73·68; H, 7·17; N, 3·44%).

The methiodide crystallized from alcohol, m.p. 255°(dec). (Found: C, 56·57; H, 5·82; N, 2·44; I, 23.21. $C_{25}H_{29}O_4N{\cdot}CH_3I$ requires: C, 56·83; H, 5·87; N, 2·55; I, 23·10%).

Sinomeninone-4-phenylether (XII)

A solution of 12 g of the benzene adduct of sinomenine-4-phenylether in 120 cc 10% HCl was heated for 2 hr on a water bath. Upon cooling, the solution was made basic with 20% Na_2CO_3 and the crystalline product washed with water and crystallized from methanol yielding 8·45 g pure sinomeninone-4-phenylether (84%), m.p. 212–214°. $[\alpha]_D^{22}$ −64·7° ± 2° (*c*, 1·043, chloroform). I.R. $\lambda_{max}^{CHCl_3}$ 3535 cm^{-1} (OH): 1678 cm^{-1} (conjugated >C=O). (Found: C, 72·37; H, 6·61; N, 3·35; OCH_3: 10·80. $C_{24}H_{25}O_4N{\cdot}1/2CH_3OH$ requires: C, 72·21; H, 6·68; N, 3·44; OCH_3, 11·42%).

The hydrochloride crystallized from 10% HCl m.p. 97° (dec). $[\alpha]_D^{20}$ −61·9° ± 2° (*c*, 0·47; alc.). (Found: C, 64·96; H, 6·39; N, 2·92; Cl, 8·19; OCH_3, 7·50. $C_{24}H_{25}O_4N{\cdot}HCl{\cdot}H_2O$ requires: C, 64·64; H, 6·33; N, 3·14; Cl, 7·95; OCH_3, 6·96%).

6,7-Diethylene glycol ketal of sinomeninone-4-phenylether (XVI)

(a) *From sinomenine-4-phenylether*. A benzene solution of 4 g of the benzene adduct of sinomenine-4-phenylether and 10 cc ethylene glycol was refluxed with 3·5 g toluene-*p*-sulphonic acid for 7 hr, with an "azeotropic" receiver to collect the volatile products. Upon cooling, 10% Na_2CO_3 was added to give a slightly alkaline reaction and the 2 layers separated. The alkaline solution was extracted with chloroform and the crude base chromatographed on alumina, the chloroform eluate yielding 3 g of the crude product. Crystallization from ethylacetate yielded 2·6 g pure diketal derivative (65%), m.p. 198–200°. $[\alpha]_D^{23}$ −37·6° ± 2° (*c*, 1·037, alc.). (Found: C, 70·32; H, 6·94; N, 2·96. $C_{25}H_{33}O_6N$ requires: C, 70·12; H, 6·94; N, 2·92%). The infra-red spectrum showed no absorption band due to enol methylether and carbonyl groups.

The methiodide was prepared in and crystallized from alcohol, m.p. 120°. $[\alpha]_D^{21}$ −21·0° ± 2° (*c*, 1·093, methanol). (Found: C, 54·81; H, 6·18; N, 2·00; I, 19·69. $C_{25}H_{33}O_6N{\cdot}CH_3I$ requires: C, 54·46; H, 5·99; N, 2·19; I, 19·85%).

(b) *From sinomeninone-4-phenylether* (XII). A benzene solution of 5 g sinomeninone-4-phenylether and 10 cc ethylene glycol was refluxed with 4 g toluene-*p*-sulphonic acid for 7 hr as described above. The reaction mixture yielded 4·76 g of the diketal derivative (81%), m.p. 198–200° and this was not depressed on admixture with the sample obtained from sinomenine-4-phenylether.

Ethylene glycol ketal of dihydrosinomenine-4-phenylether (XVII)

A benzene solution of 2·6 g dihydrosinomenine-4-phenylether and 5 cc ethylene glycol was refluxed with 2 g toluene-*p*-sulphonic acid for 7 hr, and yielded 2·9 g of the compound as a syrup (essentially quantitative). $[\alpha]_D^{17}$ −56·2° ± 2° (*c*, 1·0, alc.).

The methiodide was prepared in and crystallized from alcohol, m.p. 260° (dec). $[\alpha]_D^{24}$ −46·2° ± 2° (*c*, 1·165, alc.). (Found: C, 56·65; H, 6·13; N, 2·29; I, 21·75. $C_{27}H_{35}O_5N{\cdot}CH_3I$ requires: C, 56·66; H, 6·11; N, 2·36; I, 21·39%).

(+)-3-*Methoxy-4-phenoxy*-N-*methyl*-Δ^3-*morphinan* (X)

(a) *From sinomenine-4-phenylether* (IX). Amalgamated zinc (prepared from 20 g mossy zinc and 2 g mercuric chloride) was added in small portions to a hot solution of 3·6 g of the benzene adduct of sinomenine-4-phenylether in 25 cc conc HCl during 2 hr. The mixture was heated on a water bath with stirring for 6 hr, during which time 15 cc conc HCl was added every 2 hr. The solution was cooled to room temp, diluted with water, made basic with dil NaOH and extracted with benzene. The solvent was distilled off under red. press. and 2·7 g of product obtained. An alcoholic solution of the product was refluxed with 0·5 g hydroxylamine hydrochloride and 0·5 g sodium acetate for 1 hr. The solvent was distilled off and the residue in water made alkaline with dil NaOH and extracted with ether. The product was chromatographed on alumina and the ether eluate gave 2·43 g of a syrup (90%). $[\alpha]_D^{23}$ + 52·4 ± 3° (*c*, 0·722, alc.). The free base did not crystallize, but its methanol adduct was obtained as needles when this syrup was treated with methanol. m.p. 91–96°. $[\alpha]_D^{23}$ +51·5° ± 2° (*c*, 1·028, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1660 cm^{-1} (CH—CH). (Found: C, 76·47; H, 8·02; N, 3·51; OCH_3, 14·55. $C_{24}H_{27}O_2N{\cdot}CH_3OH$ requires: C, 76·30; H, 7·94; N, 3·56; OCH_3, 15·77%).

The methiodide was prepared in and crystallized from alcohol, m.p. 228°. $[\alpha]_D^{24}$ +34·4° ± 2° *c*, 1·016, alc.). (Found: C, 58·63; H, 6·67; N, 2·82; I, 23·43. $C_{24}H_{27}O_2N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 59·01; H, 6·60; N, 2·55; I, 23·10%).

The picrate was prepared in and crystallized from alcohol, m.p. 211–212°. (Found: C, 60·88; H, 5·44; N, 9·29. $C_{24}H_{27}O_2N{\cdot}C_6H_3O_7N_3$ requires: C, 61·01; H, 5·12; N, 9·49%).

(b) *From dihydrosinomenine-4-phenylether* (XI). 3·0 g dihydrosinomenine-4-phenylether was heated with 60 cc conc HCl and amalgamated zinc (prepared from 20 g mossy zinc and 2 g mercuric chloride) for 6 hr and yielded 2·36 g of crude product (89%). The methanol adduct m.p. 91–96° was undepressed on admixture with the sample obtained from sinomenine-4-phenylether.

(c) *From sinomeninone-4-phenylether* (XII). A mixture of 2·0 g sinomeninone-4-phenylether, 50 cc conc HCl and amalgamated zinc (prepared from 13 g mossy zinc and 1 g mercuric chloride) was heated for 6 hr on a water bath yielding 1·62 g of the crude base (91·5%). The methanol adduct m.p. 91–96° was not depressed on admixture with the sample.

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(+)-3-*Methoxy*-4-*phenoxy*-N-*methylmorphinan* (VIII)

(a) *From desmethoxydesoxodihydrosinomenine* ((+)-*tetrahydrodesoxycodeine*; VII). A pyridine solution of 5·74 g desmethoxydesoxydihydrosinomenine, i.e. (+)-tetrahydrodesoxycodeine and 6·28 bromobenzene was refluxed with 3·14 g finely powdered K_2CO_3 and 1 g copper for 15 hr. Upon cooling, the reaction mixture was treated as in the case of the Ullmann reaction of sinomenine. The benzene eluate gave 5·5 g of crude product which crystallized from pet. ether yielding 3·7 g pure (+)-3-methoxy-4-phenoxy-N-methylmorphinan (51%), m.p. 95–96°. $[\alpha]_D^{21}$ +9·5° ± 2° (*c*, 1·20, alc.). (Found: C, 79·29; H, 8·06; N, 3·76. $C_{24}H_{29}O_2N$ requires: C, 79·30; H, 8·04; N, 3·85%).

The picrate was prepared in and crystallized from alcohol, m.p. 222°. (Found: C, 60·57; H, 5·49; N, 9·30. $C_{24}H_{29}O_2N{\cdot}C_6H_3O_7N_3$ requires: C, 60·80; H, 5·44; N, 9·46%).

The methiodide was prepared in ether and crystallized from alcohol, m.p. 237–238°. $[\alpha]_D^{18}$ +6·1° ± 2° (*c*, 0·948, alc.). (Found: C, 58·75; H, 6·88; N, 2·40; I, 23·57. $C_{24}H_{29}O_2N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 58·80; H, 6·95; N, 2·54; I, 23·01%).

(b) *From* (+)-3-*methoxy*-4-*phenoxy*-N-*methyl*-Δ^x-*morphinan* (X). A solution of 1·2 g of the methanol adduct of (+)-3-methoxy-4-phenoxy-N-methyl-Δ^x-morphinan in 30 cc glacial acetic acid was hydrogenated over 50 mg Adams' catalyst at room temp. After consumption of one mole equivalent of hydrogen, the solution was filtered, concentrated, made basic with 20% NaOH and extracted with ether. The crude base was chromatographed on alumina and the ether eluate yielded 1·2 g of the saturated compound which crystallized from pet. ether yielding pure product m.p. 95–96° which was not depressed on admixture with the sample obtained by the Ullmann reaction.

(+)-3-*Methoxy*-N-*methyl*-Δ^x-*morphinan* (XIII)

A solution of 0·98 g (+)-3-methoxy-4-phenoxy-N-methyl-Δ^x- morphinan in 60 cc dry ether was added dropwise to 150 cc liquid ammonia (treated previously with a small amount of metallic sodium at −55–−60°). Another 0·3 g metallic sodium was added to this stirred solution keeping the temp at about −55°–−60°. When a blue coloration persisted for an hour, a small amount of ammonium chloride was added and the color disappeared. Liquid ammonia was evaporated and the residue was treated with water and ether and the ether extracts washed several times with dil NaOH. The ether layer gave 0·68 g of non-phenolic substance which crystallized on standing, (93%), m.p. 78–85°. Recrystallization from ether gave (+)-3-methoxy-N-methyl-Δ^x-morphinan, m.p. 90–94°. $[\alpha]_D^{20}$ +89·1° ± 2° (*c*, 0·968, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1660 cm^{-1} (CH=CH). (Found: C, 80·03; H, 8·95; N, 4·98. $C_{18}H_{23}ON$ requires: C, 80·25; H, 8·61; N, 5·20%).

The picrate was prepared in and crystallized from alcohol, m.p. 183–184°. (Found: C, 58·11; H, 5·59; N, 10·80. $C_{18}H_{23}ON{\cdot}C_6H_3O_7N$ requires: C, 57·82; H, 5·26; N, 11·24%).

The hydrobromide crystallized from hot water, m.p. 117–122°. $[\alpha]_D^{19}$ +59·0° ± 3° (*c*, 0·721, water). (Found: C, 58·67; H, 7·31; N, 3·75; Br, 22·11. $C_{18}H_{23}ON{\cdot}HBr{\cdot}H_2O$ requires: C, 58·70; H, 7·12; N, 3·80; Br, 21·70%).

The methiodide was prepared in alcohol and crystallized from alcohol–ether, m.p. 217–218° (dec). $[\alpha]_D^{21}$ +40·8° ± 2° (*c*, 1·001, alc.).

(+)-3-*Methoxy*-N-*methylmorphinan* (III)

(a) From (+)-3-*methoxy*-4-*phenoxy*-N-*methylmorphinan* (VIII). A solution of 0·97 g (+)-3-methoxy-4-phenoxy-N-methylmorphinan (VIII) in 50 cc dry ether was added dropwise to 100 cc liquid ammonia at −55–−60° and 0·37 g metallic sodium was added to this stirred solution. After an hour the reaction mixture was worked up as described for (+)-3-methoxy-N-methyl-Δ^x-morphinan (XIII) and 0·688 g of the crude base obtained (95%) with m.p. 100–106°. Recrystallization from ether gave pure (+)-3-methoxy-N-methylmorphinan, m.p. 109–111°. $[\alpha]_D^{20}$ +48·1° ± 2° (*c*, 0·915, alc.). This m.p. showed no depression on admixture of (+)-3-methoxy-N-methylmorphinan obtained from 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. (Found: C, 79·80; H, 9·28; N, 4·90. $C_{18}H_{25}ON$ requires: C, 79·66; H, 9·29; N, 5·16%).

The combined alkaline solutions were made acidic and extracted with ether. The *p*-nitrobenzoate m.p. 129–130° was identified as phenyl *p*-nitrobenzoate.

(b) *From* (+)-3-*methoxy*-N-*methyl*-Δ^x-*morphinan* (XIII). A solution of 0·18 g (+)-3-methoxy-N-methyl-Δ^x-morphinan (XIII) in 6 cc glacial acetic acid was hydrogenated in the presence of 10 mg of Adams' catalyst at room temp yielding 0·18 g of the crude base which was purified from ether. The

m.p. 105–108°, was not depressed on admixture with an authentic sample of (+)-3-methoxy-N-methylmorphinan.

(c) *From 6,7-diethylene glycol ketal of desoxysinomeninone* (XVIII). A mixture of amalgamated zinc (prepared from 6·5 g mossy zinc), 1 g of the ketal derivative and 20 cc conc HCl was heated on a water bath for 5 hr. The crude base (0·7 g) was chromatographed on alumina and the product converted to the tartrate. After several recrystallizations from alcohol, the m.p. 193–194° (dec) was not depressed on admixture with the tartrate of (+)-3-methoxy-N-methylmorphinan, 0·4 g (37%).

(d) *From 6-ethylene glycol ketal of desoxydihydrosinomenine* (XIX). A mixture of amalgamated zinc (prepared from 13 g mossy zinc), 2 g of the ketal derivative and 40 cc conc HCl was heated on a water bath for 6 hr. The crude base (1·41 g) was converted to the tartrate and recrystallized from alcohol, m.p. 192–193° (dec), 0·89 g (38%).

Desoxysinomeninone (XX)

A solution of 3 g of 6,7-diethylene glycol ketal of sinomeninone-4-phenylether (XVI) in 100 cc dry toluene was added dropwise to 300 cc liquid ammonia at −55–−60° and 0·42 g metallic sodium was added to this stirred solution and the mixture treated as usual. The crude base was chromatographed on alumina and the ether eluate gave 2·35 g of the desoxy compound, m.p. 202–206°, (97%). Recrystallization from methanol raised the m.p. to 203–206°, $[\alpha]_D^{23}$ +49·8° ± 2° (*c*, 1·088, alc.). (Found: C, 68·46; H, 7·46; N, 3·57. $C_{22}H_{29}O_5N$ requires: C, 68·19; H, 7·54; N, 3·62%).

The methiodide was prepared in and crystallized from alcohol, m.p. 249–250°. $[\alpha]_D^{18}$ +33·5° ± 2° (*c*, 1·070, alc.).

This compound was converted to desoxysinomeninone (XX) by the action of 20% HCl. The m.p. 190–192° after recrystallization from hot benzene was not depressed on admixture with the sample obtained from desoxysinomenine (XXI). $[\alpha]_D^{17}$ +49·5° ± 2° (*c*, 0·986, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 3525 cm^{-1} (OH): 1725 cm^{-1} (W): 1679 cm^{-1} (S) (conjugated >C—O). (Found: C, 72·20; H, 7·15; N, 4·79. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%).

The methiodide was prepared in and crystallized from methanol, m.p. 269–270° (dec). (Found: C, 51·51; H, 5·51; N, 3·14; I, 28·88. $C_{18}H_{21}O_3N{\cdot}CH_3I$ requires: C, 51·71; H, 5·48; N, 3·18; I, 28·76%).

Sodium–ammonia reduction of sinomenine-4-phenylether (IX)

A solution of 2 g of the benzene adduct of sinomenine-4-phenylether (IX) in 70 cc dry toluene was added dropwise to 150 cc liquid ammonia at −50–−55° and 0·7 g metallic sodium added to this stirred solution. After ½ hr the mixture was treated as usual. 1·2 g of the crude base was treated with ether and 0·42 g of a white crystalline product collected (32%).

Desoxysinomenine (XIV) crystallized from ether, m.p. 163–173° (m.p. 180–182° by monoscope). $[\alpha]_D^{20}$ −24·2° ± 2° (*c*, 1·056, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1691 cm^{-1} (conjugated C—O): 1632 cm^{-1} (enol methylether). (Found: C, 72·75; H, 7·60; N, 4·61; OCH_3, 19·94. $C_{19}H_{23}O_3N$ requires: C, 72·82; H, 7·40; N, 4·47; OCH_3, 19·81%).

The methiodide was prepared in and crystallized from alcohol, m.p. 247–248°. (Found: C, 52·61; H, 5·80; N, 3·01; I, 27·39. $C_{19}H_{23}O_3N{\cdot}CH_3I$ requires: C, 52·75; H, 5·76; N, 3·08; I, 27·87%). Treatment of desoxysinomenine (XIV) with 20% HCl gave desoxysinomeninone (XX) m.p. 190–192°.

Desoxydihydrosinomenine (XV)

This compound was obtained from the ether solution as a syrup, yield 0·7 g. The methiodide prepared in and crystallized from alcohol, melted at 222–225° and the infra-red spectrum was identical with that of desoxydihydrosinomenine obtained from dihydrosinomenine-4-phenylether (XI).

Desoxydihydrosinomenine (XV)

A solution of 2 g dihydrosinomenine-4-phenylether (XI) in 40 cc dry toluene was added dropwise to 200 cc liquid ammonia at −50–−55° and 0·6 g metallic sodium added to this stirred solution and the reaction mixture treated as usual. 1·45 g of desoxydihydrosinomenine was obtained as a syrup, (94%). I.R. $\lambda_{max}^{CHCl_3}$ 1728 cm^{-1} (C—O).

The methiodide prepared in and crystallized from alcohol, melted at 222–225°. (Found: C, 51·55; H, 6·53; N, 2·96. $C_{19}H_{25}O_2N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 52·49; H, 6·81; N, 2·78%). This methiodide was not depressed on admixture with the sample obtained from ethylene glycol ketal of desoxydihydrosinomenine.

Ethylene glycol ketal of desoxydihydrosinomenine (XIX)

A solution of 1 g 6-ethylene glycol ketal of dihydrosinomenine-4-phenylether in 20 cc dry toluene was added dropwise to 100 cc liquid ammonia at −50—−55° and 0·4 g metallic sodium added and the mixture worked up as usual. Recrystallization of 0·71 g of the crude product from ethyl acetate gave pure ethylene glycol ketal of desoxydihydrosinomenine (XIX), m.p. 177–179°. $[\alpha]_D^{24}$ +10·0° ± 2° (*c*, 1·001, alc.). (Found: C, 70·33; H, 8·37; N, 3·89. $C_{21}H_{29}O_4N$ requires: C, 70·17; H, 8·13; N, 3·90%).

The methiodide prepared in and crystallized from alcohol melted at 246–247°, $[\alpha]_D^{19}$ +3·3° ± 2° (*c*, 0·992, alc.). (Found: C, 52·60; H, 6·56; N, 2·87; I, 24·86. $C_{21}H_{29}O_4N{\cdot}CH_3I$ requires: C, 52·70; H, 6·43; N, 2·79; I, 25·31%). This ketal derivative was converted to desoxydihydrosinomenine (XXI) by treating it with 10% HCl but could not be made to crystallize.

The methiodide prepared in and crystallized from alcohol, melted at 225°. (Found: C, 52·14; H, 6·72; N, 2·75; I, 25·26. $C_{19}H_{25}O_3N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 52·49; H, 6·81; N, 2·78; I, 25·21%).

Acknowledgements—We are indebted to emeritus Prof. Ochiai of Tokyo University, Prof. Tomita of Kyoto University and Dr. Takeda, director of our laboratory for valuable discussions.

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ELIMINATION OF THE 4-HYDROXYL GROUP OF THE ALKALOIDS RELATED TO MORPHINE—II*

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Abstract—Dihydrothebaine-ϕ, dihydrothebainone-Δ^5- enol methylether and dihydrothebainone were converted to the respective 4-phenylethers by Ullmann reaction in good yields. These phenylether derivatives were reduced to 4-desoxy compounds by sodium–liquid ammonia reduction.

Clemmensen reduction of the phenylether and the desoxy derivatives gave (—)-3-methoxy-4-phenoxy-N-methyl-morphinan and (—)-3-methoxy-N-methylmorphinan respectively.

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IN a previous paper† the elimination of the 4-hydroxyl group of sinomenine and its derivatives was reported. The present paper is concerned with the synthesis of (—)-3-methoxy-N-methylmorphinan and its derivatives.

Recently, many N-methylmorphinan derivatives were synthesized from 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline derivatives by Grewe[1] and by Schnider.[2]

Among these compounds (—)-3-hydroxy-N-methylmorphinan has been found to have 3–5 times the activity of morphine as an analgesic. Elimination of the 4-hydroxyl group of thebaine derivatives may give some pharmacologically interesting compounds. The methods employed are the same as those used previously in the sinomenine series but using thebaine as a starting material.

In 1950, Bentley[3] succeeded in scission of the 4–5 oxygen bridge of thebaine (I) by the sodium–ammonia reduction and obtained dihydrothebaine-ϕ (II) in excellent yield.

Under conditions similar to those used for sinomenine, dihydrothebaine-ϕ (II) was converted to the 4-phenylether (III) in 85 per cent yield. Hydrogenation of this compound over palladium–strontium carbonate gave the 4-phenylether of dihydrothebainone-Δ^5-enol methylether (IV) and successive treatment with dilute hydrochloric acid gave dihydrothebainone-4-phenylether (V) in about 70 per cent yield based on dihydrothebaine-ϕ-phenylether (III).

The Ullmann reaction of dihydrothebainone-Δ^5-enol methylether (VI) and of dihydrothebainone (VII) gave their respective phenylethers in about 70 per cent yield. Sodium–liquid ammonia reduction of dihydrothebaine-ϕ-phenylether (III) afforded desoxydihydrothebaine-ϕ (VIII) in 90 per cent yield. After hydrogenation, this compound was treated with dilute hydrochloric acid to give desoxydihydrothebainone (IX) in 50 per cent yield. Sodium–ammonia reduction of the crude phenylether of

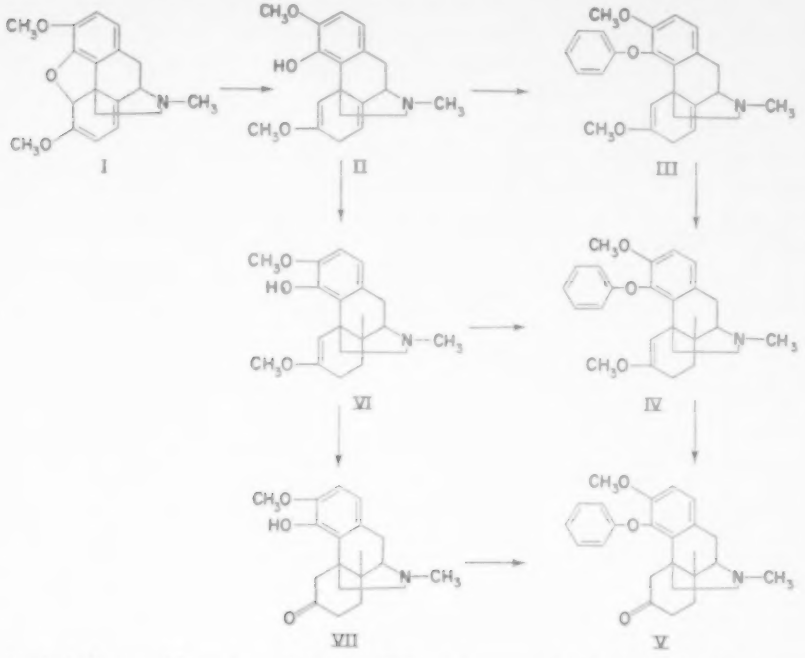
* An outline of this paper was reported at the I.U.P.A.C. Symposium on the Chemistry of Natural Products in Melbourne, Australia, August, 1960.

† Y. K. Sawa, N. Tsuji and S. Maeda, *Tetrahedron* **15**, 144 (1961).

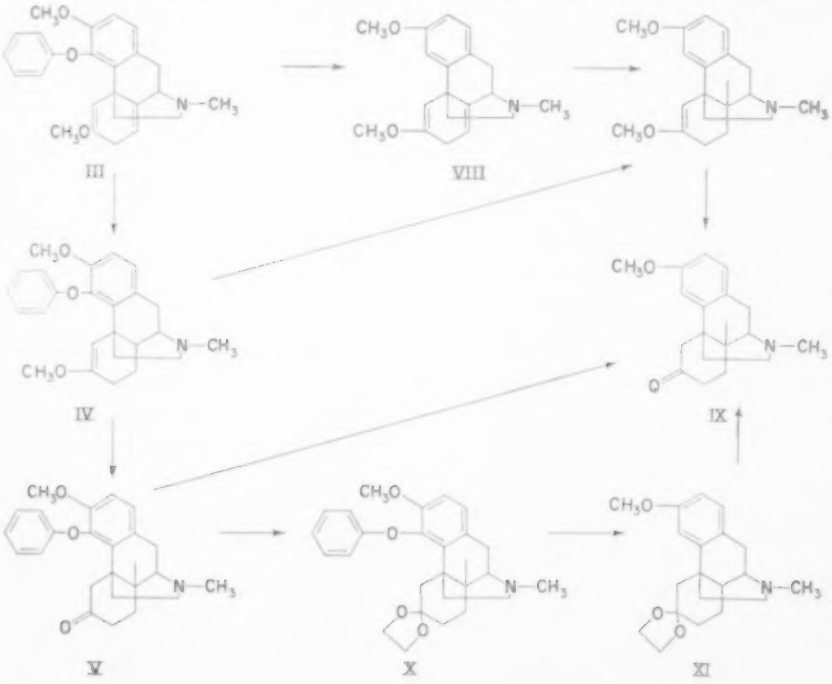
[1] R. Grewe and A. Mondon, *Chem. Ber.* **81**, 279 (1948); R. Grewe, A. Mondon and E. Nolte, *Liebigs Ann.* **564**, 161 (1949).

[2] O. Schnider and A. Grüssner, *Helv. Chim. Acta* **32**, 821 (1949): *Ibid* **34**, 2211 (1951): O. Schnider, A. Brossi and K. Vogler, *Ibid* **37**, 710 (1954): *Ibid* **33**, 1437 (1950).

[3] K. W. Bentley and R. Robinson, *Experientia* **6**, 353 (1950): K. W. Bentley, R. Robinson and A. E. Wain, *J. Chem. Soc.* **1952**, 958.

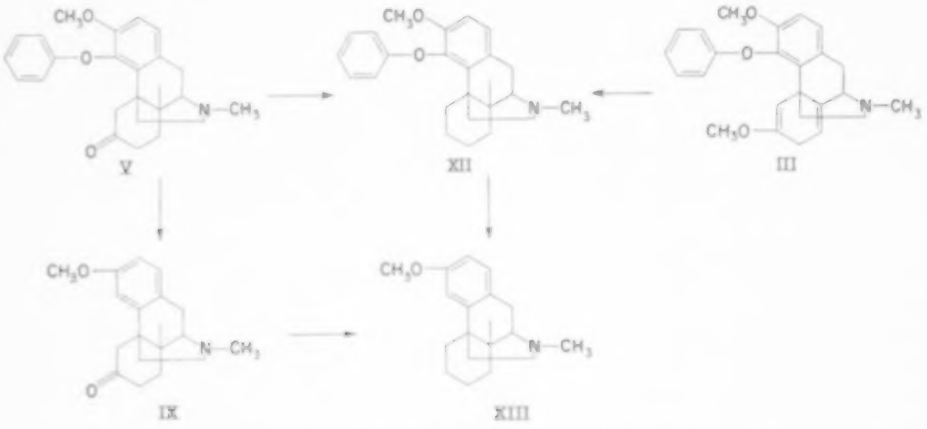


dihydrothebainone-Δ^5-enol methylether (IV) and successive hydrolysis also gave the same carbonyl compound (IX) in 85 per cent yield. Dihydrothebainone-4-phenylether (V) was treated with ethylene glycol and *p*-toluene sulfonic acid in order to protect the



6-carbonyl group and successive sodium–ammonia reduction of the product gave the ethylene glycol ketal of desoxydihydrothebainone (XI). The action of dilute hydrochloric acid on the ketal derivative gave desoxydihydrothebainone i.e. (—)-3-methoxy-6-oxo-N-methylmorphinan (IX) in 75 per cent yield based on dihydrothebainone-4-phenylether.

Sodium–ammonia reduction of dihydrothebainone-4-phenylether (V) also gave the same desoxy base, but in a poor yield. Furthermore, tetrahydrodesoxycodeine-4-phenylether (XII) was obtained from dihydrothebainone-4-phenylether (V) and dihydrothebaine-ϕ-phenylether (III) by the Clemmensen reduction in yields of 85 and 25 per cent respectively.



The 4-phenoxy group of tetrahydrodesoxycodeine (XII) was also eliminated by sodium–ammonia reduction to yield (—)-3-methoxy-N-methylmorphinan (XIII) in almost quantitative yield. The Clemmensen reduction of desoxydihydrothebainone (IX) also gave the same compound (XIII) in 55 per cent yield. A number of these new 4-desoxy compounds have been screened for analgesic and antitussive activity, but the pharmacology of these compounds will be reported elsewhere.

EXPERIMENTAL

All melting points are uncorrected. Analyses of the compounds were carried out by Messrs. K. Miyahara, Y. Daikatsu, T. Takaoka and Miss U. Kasugai of our laboratory. The infra-red spectra were determined by Messrs. Y. Matsui and M. Takasuka on a Koken D.S. 301 infra-red spectrophotometer.

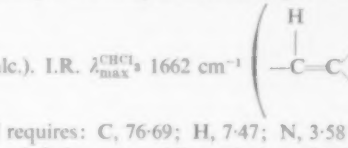
Dihydrothebaine-ϕ-4-phenylether

A pyridine solution of 47·1 g dihydrothebaine-ϕ and 5·71 g bromobenzene was refluxed for 10 hr under stirring with 32·4 g finely powdered K_2CO_3 and 4·7 g copper. The reaction mixture was treated as in the case of sinomenine-4-phenylether. The benzene eluate gave 50·38 g dihydrothebaine-ϕ-4-phenylether (86%) which crystallized from isopropanol, m.p. 135–136°, $[\alpha]_D^{28}$ +34·1° ± 2° (*c*, 0·973, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1710 cm^{-1}, 1665 cm^{-1} $\left(-\underset{H}{C}=C-OCH_3\right)$. (Found: C, 77·17: H, 7·10: N, 3·66. $C_{25}H_{27}O_3N$ requires: C, 77·09: H, 6·99: N, 3·60%).

The methiodide was prepared in and crystallized from alcohol, m.p. 191–192°. (Found: C, 57·98: H, 6·26: N, 2·12. $C_{25}H_{27}O_3N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 58·23: H, 6·28: N, 2·42%).

The picrate was prepared in ether and crystallized from alcohol, m.p. 187–188°. (Found: C, 60·05; H, 5·04; N, 9·00. $C_{25}H_{27}O_3N \cdot C_6H_3O_7N_3$ requires: C, 60·18; H, 4·89; N, 9·06%).

4-Phenylether of dihydrothebainone-Δ⁵-enol methyl ether

(a) *From dihydrothebaine-ϕ-4-phenylether.* Twenty grams of dihydrothebaine-ϕ-4-phenylether was hydrogenated over 16 g palladium–strontium carbonate (5% Pd) in 300 cc alcohol. After absorption of 1290 cc hydrogen in 15 hr and filtration of the catalyst, the solvent was removed to yield 20·2 g of crude product, m.p. 92–95°. A small sample was recrystallized from pet. ether for analysis, m.p. 106–107°. $[\alpha]_D^{32}$ −55·4° ± 1° (*c*, 2·069, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1662 cm⁻¹  . (Found: C, 76·49; H, 7·47; N, 3·46. $C_{23}H_{29}O_3N$ requires: C, 76·69; H, 7·47; N, 3·58%).

(b) *From dihydrothebainone-Δ⁵-enol methylether.* A pyridine solution of 9·45 g dihydrothebainone-Δ⁵-enol methylether and 9·4 g bromobenzene was refluxed for 15 hr with K_2CO_3 and copper. The reaction mixture was treated as usual and the product was chromatographed on alumina. The benzene eluate gave 11·28 g of a syrup which on standing solidified, m.p. 93–97°. A small sample was recrystallized from pet. ether, m.p. 106–107°. This compound was not depressed on admixture with the sample obtained from dihydrothebaine-ϕ-4-phenylether.

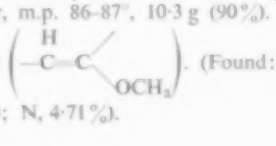
Dihydrothebainone-4-phenylether

(a) *From the phenylether of dihydrothebainone-Δ⁵-enol methylether.* A solution of 11·28 g of the crude phenylether of dihydrothebainone-Δ⁵-enol methylether in 55 cc 2 N HCl was heated for 10 min on a water-bath, cooled to room temp. and made basic with ammonia. The precipitated oil solidified on standing (8·9 g) and was recrystallized from isopropanol, 8·18 g (69% based on dihydrothebainone-Δ⁸-enolmethylether.) m.p. 145–146°. $[\alpha]_D^{29}$ +11·2° ± 2° (*c*, 0·980, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1712 cm⁻¹ (>C=O). (Found: C, 73·08; H, 7·41; N, 3·87; H_2O, 3·92. $C_{24}H_{27}O_3N \cdot H_2O$ requires: C, 72·88; H, 7·39; N, 3·45; H_2O, 4·55%).

The hydrochloride crystallized from alcohol–ethyl acetate, m.p. 276–277° (dec). (Found: C, 66·94; H, 6·90; N, 3·12; Cl, 8·23. $C_{24}H_{27}O_3N \cdot HCl \cdot H_2O$ requires: C, 66·73; H, 7·00; N, 3·25; Cl, 8·20%).

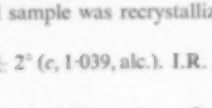
(b) *From dihydrothebainone.* A pyridine solution of 9·04 g dihydrothebainone and 9·4 g bromobenzene was refluxed for 15 hr with 12·4 g finely powdered K_2CO_3 and 1 g copper. The benzene eluate afforded 9·04 g of the crude base which recrystallized from isopropanol, m.p. 144–145°, 8·23 g (71%). The mixed m.p. with the sample prepared from the phenylether of dihydrothebainone-Δ⁵-enol methylether, was 145–146°.

Desoxydihydrothebaine-ϕ

A solution of 15 g dihydrothebaine-ϕ-4-phenylether in 150 cc toluene was added dropwise to 150 cc liquid ammonia at −50– −55°. 2·8 g metallic sodium was added to this stirred solution. After 1 hr the reaction mixture was worked up as described in the previous paper. The crude base was recrystallized from pet. ether, m.p. 86–87°, 10·3 g (90%). $[\alpha]_D^{25}$ −24·9° ± 2° (*c*, 2·113, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1707 cm⁻¹, 1666 cm⁻¹  . (Found: C, 76·99; H, 7·75; N, 4·66. $C_{19}H_{23}O_2N$ requires: C, 76·73; H, 7·80; N, 4·71%).

Desoxydihydrothebainone-Δ⁵-enol methylether

(a) *From the phenylether of dihydrothebainone-Δ⁵-enol methylether.* A solution of 10·1 g of the phenylether of dihydrothebainone-Δ⁵-enol methylether in 40 cc toluene was reduced with 1·9 g metallic sodium in 300 cc liquid ammonia. After 1 hr the reaction mixture yielded 7·7 g of crude

product (almost quantitative). A small sample was recrystallized from pet. ether to give colorless needles, m.p. 103·5–104·5°. $[\alpha]_D^{30}$ −70·5° ± 2° (*c*, 1·039, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1664 cm^{-1}  . (Found: C, 76·44; H, 8·51; N, 4·48. $C_{18}H_{23}O_2N$ requires: C, 76·22; H, 8·42; N, 4·68%).

(b) *From desoxydihydrothebaine-ϕ.* 2 g desoxydihydrothebaine-ϕ was hydrogenated over 0·25 g Adams' catalyst in 50 cc alcohol. After 22 hr and absorption of 1 mole H_2, the catalyst was removed and the filtrate concentrated to yield 2 g crude product. This base could not be crystallized but treatment with dil HCl gave 0·85 g desoxydihydrothebainone.

Desoxydihydrothebainone

(a) *From desoxydihydrothebainone-Δ^5-enol methylether.* A solution of 30·5 g desoxydihydrothebainone-Δ^5-enol methylether, m.p. 103·5–104·5°, in 150 cc 2 N HCl was heated for 10 min on a water bath. The cooled solution was diluted with NaOH until basic and the precipitated colorless solid washed with water and dried, 27·8 g (96%), m.p. 183–186°. A small sample was crystallized from alcohol for analysis, m.p. 187–188·5°. $[\alpha]_D^{23}$ −97·3° ± 2° (*c*, 2·094, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1708 cm^{-1} (>C=O). (Found: C, 76·02; H, 8·21; N, 4·80. $C_{18}H_{23}O_3N$ requires: C, 75·75; H, 8·12; N, 4·91%).

(b) *From the ketal of dihydrothebainone-4-phenylether.* A benzene solution of 3·77 g dihydrothebainone-4-phenylether and 10 cc ethylene glycol was refluxed with 3·66 g toluene-*p*-sulphonic acid for 8 hr, with an "azeotropic" receiver to collect the volatile products. After cooling, the reaction mixture was treated with 10% Na_2CO_3 until basic, washed with water and dried yielding 4·18 g of crude ketal derivative as a syrup. A solution of 2·8 g of this crude ketal in 50 cc ether was added dropwise to 100 cc liquid ammonia and the mixture treated with 0·35 g metallic sodium. The reaction mixture yielded 2·42 g of the crude desoxy base, m.p. 82–90°. A small sample was crystallized from ether for analysis, m.p. 96–97°. $[\alpha]_D^{23}$ −32·5° ± 2° (*c*, 1·046, alc.). (Found: C, 72·85; H, 8·37; N, 4·12. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·25%).

The methiodide* was prepared in and crystallized from acetone, m.p. 241–242°. (Found: C, 53·59; H, 6·87; N, 2·75; I, 25·52. $C_{20}H_{27}O_4N{\cdot}CH_3I{\cdot}1/2CH_3COCH_3$ requires: C, 54·00; H, 6·65; N, 2·80; I, 25·36%).

A solution of 1·2 g of the crude ketal of the desoxy compound in 10 cc 5% HCl was heated for several min. The reaction mixture was made basic with dil ammonia yielding 1·01 g of the colorless solid, m.p. 183–186°. The carbonyl compound recrystallized from alcohol in small plates, m.p. 187–189°. The infra-red spectrum was identical with that of the sample prepared from desoxydihydrothebainone-Δ^5-enol methylether.

(c) *From dihydrothebainone-4-phenylether.* A solution of 10 g dihydrothebainone-4-phenylether in 100 cc toluene was added dropwise to 100 cc liquid ammonia and the mixture reduced with 2·6 g metallic sodium. The reaction mixture yielded a crystalline material insoluble in the toluene solution.

The residue (6·02 g) from the toluene was crystallized from alcohol and yielded 3·5 g (48%) of colorless plates, m.p. 187–189°. This compound was identified as desoxydihydrothebainone.

The crystalline material (0·51 g), insoluble in toluene, had m.p. 201–205° and recrystallized from alcohol to give colorless prisms, m.p. 203–205°. The infra-red spectrum did not indicate the absorption band due to carbonyl group but that of hydroxyl group. (Found: C, 75·24; H, 8·74; N, 5·01. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%). It appeared to be 4-desoxydihydrothebainol.

Tetrahydrodesoxycodeine-4-phenylether

(a) *From dihydrothebainone-4-phenylether.* Amalgamated zinc (prepared from 20 g mossy zinc and 2 g mercuric chloride) was added in small portions to a hot solution of 3·0 g dihydrothebainone-4-phenylether in 25 cc conc HCl and 10 cc glacial acetic acid during 2 hr. The mixture was heated on a waterbath for 3 hr, during which time 8 cc conc HCl was added every ½ hr.

The solution was diluted, made basic with NaOH and extracted with benzene. The residue was treated with hydroxylamine in methanol and the crude product was chromatographed on alumina in

* The infra-red spectrum of this compound showed the absorption band due to carbonyl group.

ether solution to yield 2·34 g tetrahydrodesoxycodeine-4-phenylether (85%), m.p. 92–93°. $[\alpha]_D^{25}$ −6·7° ± 2° (*c*, 2·202, alc.). (Found: C, 79·13; H, 8·06; N, 3·54. $C_{24}H_{29}O_2N$ requirse: C, 79·30; H, 8·04; N, 3·85%).

The picrate crystallized from alcohol, m.p. 218–219° (dec). (Found: C, 60·91; H, 5·64; N, 9·26. $C_{24}H_{29}O_2N{\cdot}C_6H_3O_7N_3$ requires: C, 60·80; H, 5·44; N, 9·46%).

The methiodide recrystallized from alcohol, m.p. 239–240°. $[\alpha]_D^{20}$ −5·3° ± 2° (*c*, 0·781, alc.). The infra-red spectrum of tetrahydrodesoxycodeine-4-phenylether in chloroform was identical with that of desmethoxydesoxodihydrosinomenine-4-phenylether.

(b) *From dihydrothebaine-ϕ-4-phenylether*. A mixture of 5 g dihydrothebaine-ϕ-4-phenylether, amalgamated zinc (prepared from 30 g mossy zinc) and 110 cc of conc HCl was heated for 6 hr.

After treatment with hydroxylamine, 4·89 g of the crude base was chromatographed and the eluate treated with picric acid. Recrystallization of the picrate raised the m.p. to 217–218° (dec). Liberation of the picrate with dil NaOH gave 1·15 g tetrahydrodesoxycodeine-4-phenylether (25%), m.p. 89–91°. The m.p. showed no depression when mixed with the sample obtained from dihydrothebainone-4-phenylether.

(−)-3-*Methoxy-N-methylmorphinan*

(a) *From tetrahydrodesoxycodeine-4-phenylether*. A solution of 2·34 g tetrahydrodesoxycodeine-4-phenylether in 100 cc ether was added dropwise to 100 cc liquid ammonia and the mixture treated with 0·55 g metallic sodium yielding 1·75 g of crude product, m.p. 104–107°. Chromatography of this material in ether over activated alumina, raised the m.p. to 106–108° and afforded 1·70 g of the desoxy base (97%). $[\alpha]_D^{19}$ −45·9° ± 2° (*c*, 2·018, alc.).

Treatment of the base with 48% HBr gave (−)-3-hydroxy-N-methylmorphinan, m.p. 198–199°. $[\alpha]_D^{19}$* −39·8° ± 2° (*c*, 3·009, alc.). This compound was not depressed on admixture with the sample prepared from (+)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline according to Schnider.

(b) *From desoxydihydrothebainone*. A solution of 1 g desoxydihydrothebainone in 30 cc conc HCl was reduced with amalgamated zinc (prepared from 10 g mossy zinc). Treatment of the reaction mixture with hydroxylamine and additional chromatography on alumina gave 0·522 g of the desoxy base. The m.p., 108–109° was not depressed on admixture with an authentic sample of (−)-3-methoxy-N-methyl-morphinan, $[\alpha]_D^{19}$ −47·0° ± 2° (*c*, 1·965, alc.).

Acknowledgements—We are indebted to emeritus Prof. E. Ochiai of Tokyo University, Prof. M. Tomita of Kyoto University and Dr. K. Takeda, director of our laboratory for valuable discussions.

* Amylenehydrate adduct.

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ALKALOIDS FROM *ASPIDOSPERMA AUSTRALE* MÜLL. ARGOV.

THE STRUCTURE OF OLIVACINE AND *u*-ALKALOID C (GUATAMBUINE)

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Abstract—From *A. australe* the following alkaloids were isolated: from the aereal bark olivacine and (±) guatambuine; from the heartwood, olivacine and a base m.p. 186–188° present in very small amounts; from root bark, olivacine, (+) guatambuine (*u*-alkaloid C), (−) guatambuine and uleine; from root heartwood, olivacine. (±) Guatambuine is N-methyl-tetrahydro-olivacine. The products of the Hofmann degradation of the last base are identical with those obtained from uleine, a result which correlates both bases and definitely establishes the structure of (±) guatambuine (III) and olivacine (I).

Aspidosperma australe Mull. Argov. is a species with a wide distribution in South America. It is found in the northern part of Argentina, the plains of Bolivia, in Paraguay and in the Southern and Central Brazil.

The only recorded chemical study on this species is the work done by Orazi, who found aspidospermine.[1]

From plant material collected around Corumba (Brazil) and Loreto (Province of Misiones, Argentina), the following known alkaloids were isolated from *A. australe:* from the stem bark, olivacine and (±) guatambuine; from the heartwood, olivacine and a base m.p. 186–188° present in very small amounts. From root bark, olivacine, (+) guatambuine (*u*-alkaloid C) and uleine. In a new sample of root bark (−) guatambuine was found. The root heartwood yielded olivacine.

Paper chromatography showed that uleine was also present in heartwood and root wood and guatambuine in root wood. Asidospermine could not be detected in any of these sources.

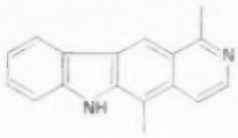
These alkaloids have been isolated from other species of Aspidosperma, olivacine from *A. olivaceum*[2] and *A. longipetiolatum*[3]; uleine from *A. ulei*[4] and *A. olivaceum*[2] and (+) guatambuine from *A. ulei* (where it was named *u*-alkaloid C)[4] and from *A. longipetiolatum*.[3]

The experiments described in this paper[5] showed that olivacine has structure (I) and is a member of the class of pyridine–carbazole alkaloids to which ellipticine (II)

[1] O. O. Orazi, *An. Asoc. Quim. Arg.* **34**, 158 (1946). Dr. Orazi has informed us that the plant specimen employed in his work has now been identified as *A. polyneuron*.
[2] J. Schmutz and F. Hunziker, *Pharm. Acta Helv.* **33**, 341 (1958).
[3] P. Carvalho-Ferreira, G. B. Marini Bettolo and J. Schmutz, *Experientia* **15**, 179 (1959); P. Carvalho-Ferreira and G. B. Marini Bettolo, *Ann. Chim.* **49**, 869 (1959).
[4] J. Schmutz, F. Hunziker and R. Hirt, *Helv. Chim. Acta* **40**, 1189 (1957); J. Schmutz and F. Hunziker, *Helv. Chim. Acta* **41**, 288 (1958).
[5] Advance information was given by M. A. Ondetti and V. Deulofeu, *Tetrahedron Letters* No. 7, 1 (1959); *Ibid.* No. 1, 18 (1960).

and methoxy-ellipticine also belong.[6] (±) Guatambuine is N-methyl-tetrahydro-olivacine (III) and is easily obtained by catalytic hydrogenation of the methiodide of olivacine.

The reverse transformation was also effected; (±) and (+) guatambuine were dehydrogenated to olivacine, by boiling with palladium in diphenyl ether, confirming again that both alkaloids have the same carbon skeleton.



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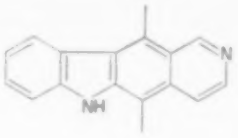

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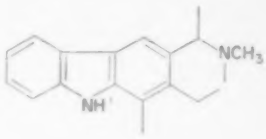

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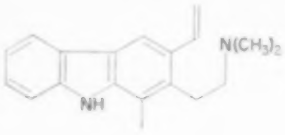

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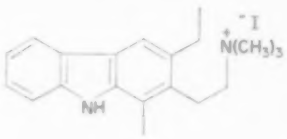

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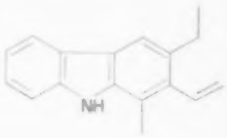

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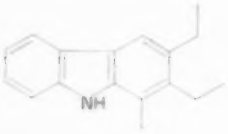

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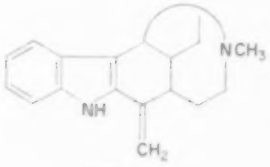

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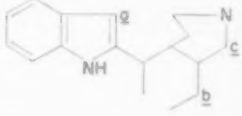

IX

The structure of guatambuine follows from its Hofmann degradation. When the methiodide of (±) guatambuine was boiled with strong alkali in ethanol, two bases were obtained that could be separated by chromatography on alumina. They were difficult to crystallize and after the separation, without any further purification, were treated with methyl iodide and transformed into two different methiodides.

One methiodide melted at 262–263° and gave a typical carbazole U.V. spectrum. The base from which this methiodide derives was a saturated compound. When it was submitted to catalytic hydrogenation prior to the treatment with methyl iodide, the same derivative melting 262–263° was obtained.

The other base gave a methiodide melting at 284–285°. This methiodide had a modified carbazole U.V. spectrum and its I.R. spectrum showed the bands characteristic of a vinyl group. When this base was first hydrogenated and treated with methyl iodide, it yielded a new methiodide, m.p. 287–288°, with a typical carbazole U.V. spectrum, showing that in the unsaturated methiodide there was conjugation between the vinyl group and the carbazol nucleus.

This new methiodide (V) was found to be identical with a methiodide m.p. 300–303°, obtained by Schmutz *et al.*[4] in their studies of the Hofmann degradation of

[6] S. Goodwin, A. F. Smith and B. C. Horning, *J. Amer. Chem. Soc.* **81**, 1903 (1959); R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, *Ibid.* **81**, 4434 (1959).

uleine. The identity of both methiodides was proved in the following way: (a) a methiodide prepared by us from uleine following the method of Schmutz and co-workers[4] had a m.p. 295–296° and when mixed with that obtained from guatambuine (m.p. 287–288°) gave a m.p. 288–290°. Both methiodides gave identical U.V. and I.R. spectra; (b) the methiodide m.p. 287–288° from guatambuine, on further degradation, as described in the experimental part, loses one atom of nitrogen and gives products (VI) and (VII), identical with those obtained from the methiodide from uleine.

Büchi and Warnhoff[7] have shown without doubt that the compound obtained after two Hofmann reactions from uleine has structure (VI) and this led to the structure (VIII) for the alkaloid. This means that the structure of the methiodide, which is a common degradation product of uleine and guatambuine must be V and that the vinyl base obtained from guatambuine methiodide is IV. This is proof of structure (III) for the last alkaloid and of structure (I) for olivacine. Structure (I) has already been suggested by Woodward and Iacobucci[8] as a result of their proposal of a common intermediate (IX) in the biogenesis of ellipticine (II) and uleine (VIII). The same intermediate could play a role in the genesis of olivacine (I) (Bond *c*—N is broken, *c* joins *a*; *b* joins N). Structure (I) was also proposed by Marini Bettolo and Schmutz[9] because of the similarity of certain physical properties of olivacine (U.V. spectrum, pK) when compared to synthetic 4-methyl-pyridocarbazole, and also on biogenetical grounds, based on the open chain intermediate proposed by Wenkert[10] as a link in the formation of indole alkaloids.

Structure (I) for olivacine has been fully confirmed by its synthesis by Schmutz and Wittwer[11] and by Wenkert.[12]

Guatambuine is the product of reduction and N-methylation of olivacine. The asymmetric carbon atom is located in a position which explains why the Hofmann degradation of (+) guatambuine gives the same inactive methiodide (V) as the racemic base. It is interesting that in *A. australe* two optical isomers and the racemic form of guatambuine have been found. While reduction of the pyridine ring may be a non-enzymatic process (which could explain the formation of the racemic form), it is obvious that this is not the case for the N-methylation, which must proceed through some specific enzyme system present in the plant.

EXPERIMENTAL

All m.p. are uncorrected and were determined in the Kofler block, except when specified. Paper chromatography was employed to follow the distribution of alkaloids in the extracts and in the fractions eluted in column chromatography. The system used was a mixture of methyl-isobutyl-ketone: butanol (7:3) saturated with McIlvaine buffer, pH 4. The R_f of the alkaloids were: olivacine: 0·13; guatambuine (*u*-alkaloid C): 0·39; uleine: 0·69. Dragendorff reagent was used to develop the spots. Ultra-violet spectra, except when noted, were recorded in absolute ethanol.

Extraction of the alkaloids

Root bark. Two kilogrammes of ground root bark were well extracted with 4·5 l. methanol, repeating the extraction five times, and a sixth time with methanol containing 2% acetic acid. The

[7] G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.* **81**, 4433 (1959).
[8] R. B. Woodward and G. A. Iacobucci, Private communication
[9] G. B. Marini Bettolo and J. Schmutz, *Helv. Chim. Acta* **42**, 2146 (1959).
[10] E. Wenkert, *Experientia* **15**, 165 (1959); E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.* **81**, 1474 (1959).
[11] J. Schmutz and H. Wittwer, *Helv. Chim. Acta* **43**, 793 (1960).
[12] E. Wenkert, Paper presented at the IUPAC Symposium: *The Chemistry of Natural Products*, Australia, August 1960; *J. Amer. Chem. Soc.* In press.

combined methanolic extracts were concentrated in vacuum to 600 ml and poured with good agitation into a mixture of 1200 ml water and 200 ml acetic acid. An insoluble product appeared which was filtered (Super-cel filter-aid), and the residue was washed well with 15% acetic acid.

The filtrate was extracted twice with petroleum ether (b.p. 40–60°), cooled to 5° and made alkaline to pH 10–11 with 50% sodium hydroxide, avoiding an increase of temperature. A gummy precipitate formed, which was separated from the solution. The alkaline solution was extracted with ether until it gave a negative Mayer's test.

The gummy precipitate was shaken with ether several times. The ethereal extracts were joined (6 l. in total), filtered, dried with sodium sulfate and concentrated to 400 ml. A yellow solid precipitated, which after filtering and drying weighed 4 g, m.p. 309–314°. The filtrate was again concentrated to 100 ml, when a new yellow precipitate was formed and collected, 1·1 g, m.p. 220–240°. The filtrate was then concentrated to dryness, the residue weighing 10 g.

The insoluble residue from the gummy precipitate, after the extraction with ether, was dissolved in a mixture of 600 ml water and 100 ml acetic acid, filtered from an insoluble residue and the filtrate made alkaline to pH 10–11, when a precipitate formed again. Without separation, precipitate and solution were extracted with ether and the process described above was repeated.

On concentration the ethereal extract yielded a first crop of yellow crystals that after well washing with chloroform, weighed 507 mg, and melted 308–312°. On further concentration, a second crop of 91 mg, m.p. 234–237°, was collected. On evaporation to dryness, a residue of 1500 mg was obtained.

Olivacine (I). The two batches of yellow crystals melting 308–314° were united and recrystallized several times from boiling ethanol. Yellow short prisms melting 314–316°, $(\alpha)_D^{24°} \pm 0°$ (Pyridine). U.V. spectrum: λ_{max} 224 mμ (ε 24,300); 238 mμ (21,300); 276 mμ (50,600); 287 mμ (71,400); 292 mμ (67,000); 314 mμ (4600); 329 mμ (6250); 375 mμ (4600). In acid (HCl) absolute ethanol λ max 242 mμ (28,600); 306 mμ (77,000); 350 mμ (6200). (Found: C, 82·8; H, 5·7; N, 11·3. Calc. for $C_{17}H_{14}N_2$: C, 82·8; H, 5·7; N, 11·3).

All these data are in agreement with the properties of olivacine described by Schmutz and Hunziker.[2]

These data are almost identical with those of ellipticine, but I.R. and NMR-spectra of both bases were different.[3]

(+) *Guatambuine* (u-*alkaloid* C) (III). Recrystallization of the 1·1 g of the crude product melting 220–240° described above, from ethanol 95%, gave crystals with m.p. 235–237°. They were mixed with those melting 234–235° from the second batch and recrystallized (700 mg) several times from ethanol. Long prisms (32 mg) melting 245–248°. $(\alpha)_D^{28°}$ +112° ±3° (*c*, 0·485. Pyridine). U.V. spectrum λ_{max} 240 mμ (ε 41,300); 250 mμ (31,300); 262 mμ (22,700); 299 mμ (19,300); 330 mμ (4300). No displacement of the bands was observed in acid absolute ethanol. I.R. spectrum in potassium bromide was identical to the I.R. spectrum of (+) guatambuine (*u*-alkaloid C). (+) Guatambuine was also obtained when 10 g of the residue left on evaporation of the ethereal extracts, from which olivacine and crude (+) guatambuine have already been separated, were dissolved in 20 ml warm benzene and the solution was cooled. Two hundred and fifty miligrammes of crystals m.p. 227–231° were obtained, which on recrystallization from ethanol melted 243–244° and were characterized as (+) guatambuine.

(+) *Uleine* (VIII). The benzene solution remaining after the separation of (+) guatambuine was chromatographed on 340 g of alumina (Woelm, activity II–III) and eluted with benzene, benzene chloroform, chloroform and chloroform–methanol. When chloroform was employed, fractions giving on paper chromatography one alkaloidal spot, R_f 0·69, were collected. On concentration of those fractions, crystals melting 72–76° (Kofler) and 118–121° (capillar) were obtained. $(\alpha)_D^{25°}$ +11·5 chloroform. U.V. spectrum: λ_{max} 307–308 mμ (ε 17,000); 316 mμ (17,000). Schmutz *et al.*[4] give a m.p. 76–80° with further solidification and melting at 115–118°.

Uleine hydrochloride. Prepared as described[4] it had a m.p. 239–241° in agreement with the m.p. 241–242° given in the literature. U.V. (ethanol 95%) λ_{max} 308–309 mμ (ε 19,300). (Found: C, 68·1; H, 7·7; N, 9·2. Calc. for $C_{18}H_{23}N_2Cl,H_2O$: C, 67·4; H, 7·8; N, 8·7).

The methiodide melted 204–206°, as described for uleine methiodide.[4]

Root wood. Olivacine. Three hundred grammes of the heartwood from the root of *A. australe* was extracted and worked as described from the root's bark. Pure olivacine (150 mg) m.p. 315–317° were isolated. The residues remaining after the removal of olivacine gave on paper chromatography spots corresponding to olivacine, guatambuine and uleine, and were not further examined.

Stem bark. *Olivacine* (±) *guatambuine and uleine*. Ground aereal bark (1·8 kg) from *A. australe* were extracted as has been described for the root's bark. The ethereal extract on first concentration gave 7·05 g of crude olivacine (m.p. 308–314°) which was identified in the usual way.

On further concentration, another crop of crystals melting 210–220° (795 mg) was obtained. Evaporation was continued to dryness, leaving a residue of 4·59 g. When this residue was treated with chloroform, the largest part dissolved, leaving an insoluble portion of 380 mg (m.p. 218–222°), which was united to the second crop. On several recrystallizations from ethanol 95%, 240 mg of long prisms, m.p. 227–228°, were obtained, $(\alpha)_D^{25°} \pm 0°$ U.V. spectrum λ_{max} 240 mμ (ε 41,000); 250 mμ (30,700); 262 mμ (22,700); 299 mμ (19,800); 330 mμ (4370). I.R. spectrum, recorded on a potassium bromide pellet, was identical to that of (+) guatambuine.

The remaining chloroform solution was then subjected to chromatography in a column containing 140 g of neutral alumina and eluted with chloroform containing increasing amounts of methanol. The first fractions eluted with chloroform–0·2% methanol, gave on evaporation and recrystallization from methanol, 14 mg of a base m.p. 74–80° (104° capillary), which gave a hydrochloride m.p. 239–241° (sintering from 234°) which did not depress the m.p. of pure uleine hydrochloride. The U.V. spectra were also identical. The middle and last fractions, eluted with chloroform–0·2% methanol, gave a spot showing the presence of guatambuine. They were collected, evaporated and recrystallized from 95% ethanol; long prisms melting 225–227°; $(\alpha)_D^{25°} \pm 0°$. U.V. spectrum identical to (±) guatambuine.

Root bark. (−) *Guatambuine*. A sample of 2 kg of root bark of *A. australe* collected near Corumbá (Brazil) was extracted and processed as described. The first crop of crystals from the ether extracts yielded 6 g of rather pure olivacine m.p. 316–320°, and the second crop, 1·65 g of impure crystals, melting 213–233°. The last crystals after several crystallizations from ethanol 95%, gave 520 mg of long prisms m.p. 247–248°. $(\alpha)_D^{26°} -106° \pm 2°$ (Pyridine). U.V. spectrum λ_{max} 240 mμ (ε 41,000); 250 mμ (31,000); 262 mμ (22,200); 299 mμ (19,200).

Twenty-five milligrammes of the above base, mixed with the same amount of (+) guatambuine, gave on crystallization from ethanol, 35 mg of the racemic base. M.p. 224–225°. $(\alpha)_D^{29°} \pm 0°$. From the mother liquors of the obtention of (−) guatambuine, 40 mg of racemic (±) guatambuine were obtained. M.p. 224–225°; $(\alpha)_D^{29°} \pm 0°$. The residue of the ether extract, after separation of the olivacine and guatambuine, showed on paper chromatography the presence of those bases and uleine. It was not further examined.

Heartwood. Olivacine, base m.p. 186–188°. Two kilogrammes of well ground heartwood were extracted with methanol and worked up in the usual way. The ether extracts on concentration yielded 460 mg of impure olivacine, m.p. 306–312°, which after several recrystallizations from ethanol 95°, 250 mg of pure olivacine with m.p. 315–317° were obtained. After separation of the olivacine, the ether solution was evaporated to dryness and a residue of 3·5 g was obtained. This residue was treated with chloroform, filtered from an insoluble crystalline fraction, consisting of impure olivacine (217 mg, m.p. 307–310°) and the chloroform solution was chromatographed on a column of 80 g of alumina (activity II–III).

The first fractions eluted with chloroform gave on paper chromatography one spot, with R_f 0·62 which was different from the usual alkaloids. Evaporation of these fractions gave a very small amount of a base, which recrystallized several times from methanol, melted 186–188°, with λ_{max} 305 mμ (ε 17,000, calculated for a molecular weight 266 identical to uleine), which gives a yellow brown colour with Keller's reagent, a weak violet colour with ceric (III) sulphate and a permanent pink colour with concentrated sulphuric acid. U.V. spectrum and colour reactions are very similar to those of uleine.

Paper chromatography of the solutions left after separation of the crystalline alkaloids showed that uleine was present in the extracts.

Olivacine methiodide. Five hundred milligrammes of olivacine were dissolved in the minimum amount of boiling ethanol 95% and 5 ml methyl iodide added. The olivacine methiodide starts to precipitate in crystalline condition very soon. After 30 min the suspension was cooled and 600 mg of yellow long prisms collected. Recrystallization from methanol gave long prisms melting above 340°, with darkening from 315° (Found: C, 55·2; H, 4·4; N, 7·4; I, 32·1. $C_{17}H_{14}N_2.CH_3I$ requires C, 55·6; H, 4·4; N, 7·22; I, 32·6).

N-*methyl-tetrahydro-olivacine or* (±) *guatambuine* (III). Four hundred milligrammes of olivacine methiodide were suspended in 300 ml ethanol 95%, 80 mg of platinum oxide catalyst added and

reduced for 4 hr at 3 atm, the solid dissolving in about 2·5 hr. After filtering, the solution was concentrated to 25 ml, 275 ml water added, alkalinized with 2 N sodium carbonate and extracted with ether. The ether extract was well dried, evaporated, and the residue, when crystallized from ethanol 95%, gave 201 mg of a crude product melting 220–223°. After several recrystallizations from ethanol, it melted at 223–225°. Its U.V. spectrum had λ_{max} 240 mμ (ε 41,100); 250 mμ (30,700); 262 mμ (22,200); 299 mμ (19,200); 330 mμ (4120). With ethanol hydrochloric acid, the typical hyperchromic effect given by guatambuine was observed, without displacement of the maxima. I.R. spectrum identical to (±) guatambuine. (Found: C, 82·3; H, 7·9; N, 10·6; NCH_3, 5·3; $C(CH_3)$, 11·1; N.E., 262. $C_{18}H_{20}N_2$ requires C, 81·7; H, 7·6; N, 10·6; NCH_3, 5·6; 1 $C(CH_3)$, 11·3; N.E., 264).

Olivacine by dehydrogenation of (+) *guatambuine*. One hundred and twenty-five milligrammes of Adams platinum catalyst were suspended in 5 ml diphenyl ether and reduced. One hundred milligrammes of (+) guatambuine was added and while nitrogen was bubbled the suspension was boiled for 80 min. It was then cooled, ether and 2 N hydrochloric acid were added until two phases formed, and the water phase was well extracted with ether. It was then made alkalien to pH 11 and extracted again with ether. This second ether extract was dried, evaporated, and the crystalline residue suspended in chloroform and filtered. The 25 mg of crude crystals collected were recrystallized from ethanol; m.p. 313–316°. They were identified as olivacine by mixed m.p. and U.V. spectrum.

(±) *Guatambuine methiodide*. To 1·1 g of (±) guatambuine dissolved in boiling ethanol, 10 ml of methyl iodide were added and boiling continued for 30 min. After cooling, 1·5 g of long prisms could be collected. M.p. 299–301°, which was not changed by further crystallization. (Found: N, 6·8; I, 30·8. $C_{18}H_{20}N_2.CH_3I$ requires: N, 6·8; I, 31·2).

Hofmann degradation of (±) *guatambuine methiodide*. Guatambuine methiodide (1·71 g) was suspended in 400 ml ethanol containing 40 g of potassium hydroxide and boiled for 6 hr. The solution was then concentrated *in vacuo* to 50 ml, 350 ml of water were added and extracted with ether. The ether extracts, after washing with water and drying, were concentrated to dryness, when a residue of 1·24 g was obtained. Paper chromatography showed the presence of two bases, which were dissolved in chloroform and submitted to column chromatography, on 80 g of alumina.

The column was first eluted with chloroform and then with chloroform containing increasing amounts of methanol. When chloroform with 0·05% methanol was employed, the first fractions contained a base which gave a spot with R_f 0·61. When the methanol content was increased (0·5%) a new base, with R_f 0·34, was eluted.

The fractions containing the first base were joined and evaporated, giving a syrup which was dissolved in a small amount of ethanol, an excess of methyl iodide added and refluxed for 15 min. Five hundred and sixty-seven milligrammes of crude methiodide, m.p. 257–258° were obtained. After several recrystallizations from ethanol 95%, it gave long prisms melting 262–263°; λ_{max} 240 mμ (ε 44,800); 250 mμ (32,600); 260 mμ (20,900); 297 mμ (16,700). When this same base was subjected without further purification to hydrogenation with Adams catalyst in ethanol and treated with methyl iodide, the same methiodide product was obtained (Mixed m.p.; U.V. spectrum). (Found: C, 56·9; H, 6·2; N, 6·4; I, 30·5. $C_{20}H_{25}IN_2$ requires: C, 57·1; H, 6·0; N, 6·6; I, 30·1).

The fractions containing the base with R_f 0·34 were also evaporated and the residue boiled with methyl iodide in ethanol. Three hundred and ninety-two milligrammes of *methiodide* were obtained, m.p. 278–279°. Recrystallized several times from 95% ethanol, long prisms m.p. 284–285° were collected. U.V. spectrum λ_{max} 241–242 mμ (ε 39,000); 280 mμ (26,800). (Found: C, 57·4; H, 5·7; N, 6·9; I, 30·3. $C_{20}H_{25}I\,N_2$ requires: C, 57·1; H, 6·0; N, 6·6; I, 30·1).

When the residue obtained by evaporation of the fractions with base R_f 0·34 was hydrogenated with Adams catalyst in ethanol and then treated with methyl iodide, the methiodide (V) after several recrystallizations from ethanol melted at 287–288°. U.V. spectrum λ_{max} 240 mμ (ε 47, 500); 250 mμ (31,600); 260 mμ (20,000); 297 mμ (21,200). (Found: C, 57·1; H, 6·4; N, 6·2; I, 30·3. Calc. for: $C_{20}H_{27}IN_2$: C, 56·8; H, 6·4; N, 6·6; I, 30·0).

This methiodide did not depress the m.p. and gave a spectrum identical with that of the methiodide obtained by subjecting uleine methiodide to Hofmann degradation according to Schmutz *et al.*[4] who give m.p. 300–302°.[18]

Hofmann degradation of the methiodide m.p. 287–288°. Three hundred and fifty milligrammes of

[18] Prof. G. Büchi has kindly informed us that in his laboratory a m.p. 281–285° (Kofler) was observed for this methiodide when recrystallized from ethanol–water.

the methiodide when treated as described by the Swiss authors[4] gave 120 mg of the crystalline methine m.p. 66–68° (VI). U.V. spectrum λ_{max} 248 mμ (ε 43,300); 299 mμ (19,500). (Found: C, 85·9; H, 8·0; N, 5·9. Calc. for $C_{15}H_{17}N$: C, 86·7; H, 7·3; N, 5·9).

This compound gave no depression in the m.p. when mixed with the similar compound obtained from uleine (m.p. 69–70·5°). I.R. spectra were identical.

Hydrogenation of the last compound and purification of the reduced product by column chromatography on alumina gave a substance m.p. 83–85° (VII). λ_{max} 240 mμ (ε 45,100); 248 mμ (30,800); 261 mμ (18,700); 298 mμ (19,600).

This substance did not depress the m.p. when mixed with the compound obtained from uleine (m.p. 76·5–77°). U.V. and I.R. spectra were identical.

Hofmann degradation of (+) guatambuine. The methiodide of (+) guatambuine m.p. 301–302° $(\alpha)_D^{22°}$ +47·0° (Pyridine:water, 5:1) was treated exactly as described for the methiodide of the racemic base. Two bases were obtained with R_f 0·61 and 0·34, which on treatment with methyl iodide gave two methiodides m.p. 258–260°, $(\alpha)_D^{22°}$ ±0° and m.p. 284–285°; $(\alpha)_D^{22°}$ ±0° identical to those from the degradation of (±) guatambuine methiodide. (No depression in m.p. and identical U.V. spectra.)

Acknowledgements—We thank Prof. R. B. Woodward for information on the proposed structure of olivacine; Prof. G. Büchi for the generous gift of several of the compounds derived from uleine and for checking some mixed m.p. and I.R. spectra; Dr. R. H. F. Manske for kindly providing us with different samples of pyridine–carbazoles; Mr. J. F. Alicino and Dr. N. H. Coy, the Squibb Institute for Medical Research, New Brunswick, N.J., for the microanalysis and I.R. spectra.

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MINOR ALKALOIDS OF *ASPIDOSPERMA SUBINCANUM* MART.: ISOLATION, STRUCTURE PROOF AND SYNTHESIS OF 1,2-DIHYDRO-ELLIPTICINE, 1,2-DIHYDRO-ELLIPTICINE METHONITRATE AND ELLIPTICINE METHONITRATE

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(*Received* 28 *March* 1961)

Abstract—Three alkaloids named in the title were isolated from the Peruvian plant "Quillo-bordon." The structures assigned were confirmed by partial syntheses.

PLANTS of the genus *Aspidosperma* have been searched intensively for alkaloids of possible therapeutic value. In recent years a number of new bases have been isolated, and the structures of some of them are now known.[1-6] An examination of the Peruvian plant "Quillo-bordon" tentatively identified as *Aspidosperma subincanum* Mart.[7] has shown that two major alkaloids present are N-methyl-tetrahydro-ellipticine (X) and ellipticine[8] (XI).

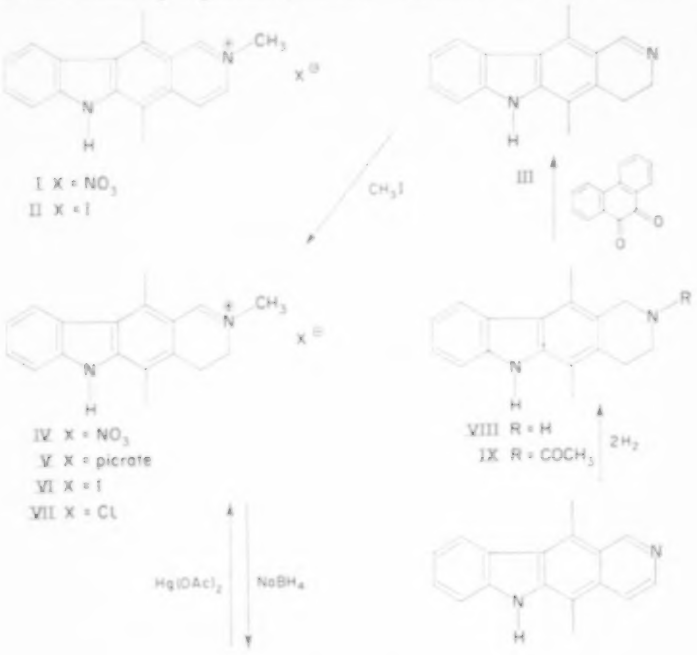
We now wish to record our observations on three minor alkaloids of the same plant and will start with a discussion of the quaternary bases whose presence had been indicated earlier.[8] Crystallization of the crude nitrates from aqueous isopropyl alcohol furnished yellow needles m.p. 300–317° (dec.). Paper chromatographic analysis revealed two major components which were subsequently separated on a preparative scale. The ultraviolet spectrum (see experimental section) of one component m.p. 293–304° (dec.) was essentially identical with that of ellipticine methiodide[3] (II) and indicated the presence of identical cations in the two salts. An authentic sample of ellipticine methonitrate (I) prepared from the methiodide by ion exchange with Dowex-1 (nitrate form) exhibited identical infrared and ultraviolet spectra. Identity was confirmed by R_f values, melting point and mixture melting point comparisons.

Combustion analyses of the second nitrate (IV) and the corresponding picrate (V) both agree with formula $C_{18}H_{19}N_2^{\oplus}$ and the ultraviolet spectrum (see experimental section) of the nitrate is strikingly similar to that of the dihydropyridocarbazole

* National Institutes of Health Postdoctoral Fellow 1960.

[1] H. Lehner and J. Schmutz, *Helv. Chim. Acta* **44**, 444 (1961) and eight earlier papers.
[2] M. A. Ondetti and V. Deulofeu, *Tetrahedron Letters* No. 1, 18 (1960); *Ibid.* No. 7, 1 (1959).
[3] S. Goodwin, A. F. Smith and E. C. Horning, *J. Amer. Chem. Soc.* **81**, 1903 (1959).
[4] B. Gilbert, L. D. Antonaccio, A. A. P. G. Archer and C. Djerassi, *Experientia* **16**, 61 (1960).
[5] R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, *J. Amer. Chem. Soc.* **81**, 4434 (1959).
[6] G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.* **81**, 4433 (1959).
[7] We are indebted to Mr. Allen for providing the plant material which was collected near Iquitos, Peru and to Dr. L. Nickell for the botanical identification.
[8] F. A. Hochstein, A. M. Paradies and R. B. Woodward, unpublished results.

(XIV)[9] in acid solution. Further, strong infrared absorption at 1645 cm^{-1} agrees with the presence of a $C{=}\overset{\oplus}{N}-$ system. These data indicate that the new alkaloid is either N-methyl-1,2-dihydro-olivacine or N-methyl-1,2-dihydro-ellipticine (IV). Reduction of the nitrate with sodium borohydride in aqueous solution yielded a tertiary base which was identical in every respect with N-methyl-tetrahydro-ellipticine (X). Structure IV was confirmed by a partial synthesis. Oxidation of X with mercuric acetate



[9] G. B. Marini-Bettolo and J. Schmutz, *Helv. Chim. Acta* **42**, 2146 (1959); R. H. F. Manske and M. Kulka, *Canad. J. Res.* **27B**, 291 (1949); *J. Amer. Chem. Soc.* **72**, 4997 (1950).

produced an acetate which was not characterized but converted directly to the corresponding nitrate. This material was identical with the natural salt (IV).

We next investigated the tertiary bases of *Aspidosperma subincanum*. The ultraviolet spectrum of one base (m.p. 293–296°) in acid solution was essentially identical with that of 1,2-dihydro-ellipticine methonitrate (IV). Consequently the two alkaloids contain identical chromophores and we simply had to place a C_2H_5 residue to arrive at the complete structure. Alkylation with methyl iodide in acetone solution furnished a methiodide (VI). This was converted to the corresponding methochloride which was identical in every respect with an authentic sample of 1,2-dihydro-ellipticine methochloride (VII) prepared from the nitrate (IV) by ion exchange. This correlation demonstrates structure III for the new alkaloid. Its structure was confirmed by a partial synthesis. Catalytic reduction of ellipticine (XI) over a platinum catalyst in ethanol solution afforded an air sensitive substance exhibiting ultraviolet light absorption typical of a carbazole. It was characterized by a stable N-acetyl derivative (IX) identified as such by strong infrared absorption at 1630 cm^{-1}. The reduction product, therefore, is 1,2,3,4-tetrahydro-ellipticine (VIII). Dehydrogenation with 9,10-phenanthraquinone in *o*-dichlorobenzene[10] at 120° yielded a yellow substance m.p. 296–300° (dec.). Identity with natural 1,2-dihydro-ellipticine (III) was established by comparison of infrared and ultraviolet spectra, R_f value and mixture melting point.

Both the melting point and infrared spectrum of 1,2-dihydro-ellipticine (III) are different from those reported for *u*-alkaloid D, m.p. 308–312° (dec.) a minor constituent of *Aspidosperma ulei* Mgf.[11] An earlier investigation revealed that this elusive base is a derivative of XIV[9] and when it was found to be different from 1,2-dihydro-olivacine (XII) the investigators assumed its identity with 1,2-dihydro-ellipticine (III).[12] We have sent a small sample of synthetic III to Dr. J. Schmutz, Berne, and he kindly informed us that a careful reexamination of *u*-alkaloid D by thin-layer chromatography on silica gel revealed the presence of two constituents which are identical with 1,2-dihydro-olivacine (XII) and 1,2-dihydro-ellipticine (III) respectively.[13]

In view of the synthesis of ellipticine by Woodward, Iacobucci and Hochstein[5] the partial routes described in this paper may be considered in a formal sense as total syntheses of these new bases.

Finally, we were able to isolate a very small quantity of olivacine (XIII) from the alkaloid fraction of *Aspidosperma subincanum*.

EXPERIMENTAL*

Isolation of 1,2-*dihydro-ellipticine methonitrate* (IV) *and ellipticine methonitrate* (I). The total dried methanolic extracts of Quillo-bordon bark were dissolved in 20% aqueous methanol, made

* Melting points were observed in evacuated capillaries and are uncorrected. Ultraviolet spectra were obtained with a Beckman DK-2 spectrophotometer. Infrared spectra were recorded with a Baird-Atomic model AB-2 spectrophotometer using a beam condensing unit utilizing silver chloride lenses. Band centers are accurate to 5 cm^{-1} at wave numbers below 1500 cm^{-1} and are followed parenthetically by the observed percent transmission. R_f values are given for two systems: (1) methylethyl ketone saturated with water (MEK) and (2) butanol–acetic acid–water (4:1:5) upper phase (BuOH). Flow rates are also given relative to ellipticine methonitrate (R_e) which was chosen as the standard compound for this series. Standard conditions for paper chromatographic separations were: freshly distilled methylethyl ketone saturated with water, temperature 19°, and Whatman 3 mm paper prewashed with methanol and methylethyl ketone. The elemental analyses were carried out by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark and Dr. S. M. Nagy and associates, M.I.T.

[10] L. M. Jackman in R. A. Raphael, E. C. Taylor, and H. Wynberg, *Advances in Organic Chemistry: Methods and Results* Vol. II, p. 340. Interscience, New York (1960).
[11] J. Schmutz and F. Hunziker, *Helv. Chim. Acta* **41**, 288 (1958).
[12] J. Schmutz and H. Wittwer, *Helv. Chim. Acta* **43**, 793 (1960).
[13] We thank Dr. J. Schmutz for his collaboration. His findings are summarized in ref. 1.

basic and extracted with chloroform to remove tertiary bases. Further extraction of the basic aqueous phase with n-butanol yielded a mixture of crude quaternary bases which was converted to a mixture of yellow crystalline nitrates. Crystallization of the crude nitrates from 2-propanol-water gave bright yellow needles, m.p. 300–317° (dec.). Paper chromatographic analysis of this material employing a system of methylethyl ketone saturated with water indicated the presence of two major components (R_f 0·15 and 0·23). A preparative scale paper chromatographic separation (265 γ/cm) of 80 mg of the crude mixture was carried out. Elution of the component lying between R_f values 0·10 and 0·16 with methanol followed by concentration, filtration and crystallization from methanol gave 6 mg of bright yellow needles. One further crystallization from methanol, an additional paper chromatographic separation (140 γ/cm), isolation and two recrystallizations from methanol afforded (3 mg) ellipticine methonitrate (I), m.p. 293–304° (dec.); R_f^{MEK} 0·15, R_f^{BuOH} 0·71; λ_{max}^{MeOH} 423, 356, 307, 249 and 241 mμ (log ε 3·68, 3·72, 4·86, 4·36 and 4·38 resp.); ν_{max}^{KBr} 1645(53), 1605 (17), 1588 (41), 1500(60), 1460(39), 1415(11), 1385(2), 1320(7), 1245(14), 1190(35), 1115(52), 825(58), 805(44), 755(20), 715(41).

This material was identical in infrared and ultraviolet spectra, m.p., mixed m.p. and R_f value with an authentic sample of ellipticine methonitrate prepared from ellipticine methiodide[3] by ion exchange with Dowex-1 (nitrate form).

A component lying between R_f values 0·17 and 0·25 was eluted with methanol. The methanol extracts were concentrated under reduced pressure and the residue crystallized from methanol giving 24 mg of pale yellow needles. Two recrystallizations from acetone–water followed by two further recrystallizations from methanol gave (15 mg) 1,2-*dihydro-ellipticine methonitrate* (IV), m.p. 301–303° (dec.); R_f^{MEK} 0·23, R_q^{MEK} 1·53; λ_{max}^{MeOH} 382, 313, 302, 281, 271(*sh*), 244(*sh*), and 236 mμ (log ε 4·43, 4·30, 4·18, 4·64, 4·46, 4·30, and 4·45 resp.); ν_{max}^{KBr} 1645(29), 1595(32), 1575(21), 1500(57), 1442(45), 1410(34), 1375(6), 1330(6), 1250(29), 1210(30), 822(60), 778(47), 750(26). (Found: C, 66·61; H, 5·79; N, 13·07. $C_{14}H_{19}N_3O_3$ requires: C, 66·44; H, 5·88; N, 12·91%).

1,2-*Dihydro-ellipticine methopicrate* (V). 1,2-Dihydro-ellipticine methonitrate (100 mg) was dissolved in 5 ml of hot water and mixed with a solution of 100 mg of picric acid in 5 ml of hot water. An immediate amorphous precipitate formed which was filtered and washed with hot water. Three recrystallizations from acetone–water afforded (98 mg) 1,2-*dihydro-ellipticine methopicrate* (V) as large bright yellow needles, m.p. 273–275° (dec.). (Found: C, 58·93; H, 4·24; N, 14·22. $C_{21}H_{21}N_6O_7$ requires: C, 58·65; H, 4·31; N, 14·25%).

Isolation of 1,2-*dihydro-ellipticine* (III). A crude fraction (60 mg) obtained during the column chromatography of the residues isolated from the mother liquors remaining from the crystallization of N-methyl-tetrahydro-ellipticine (X)[4] was subjected to further purification. Two successive chromatograms employing "Woelm" almost neutral, activity 1, alumina (elution with chloroform) followed by recrystallization from chloroform–methanol gave (26 mg) 1,2-*dihydro-ellipticine* (III), m.p. 281–283° (dec.). This material was shown to contain a small amount of ellipticine (XI) by paper chromatographic examination.

A small quantity of the partially purified, 1,2-dihydro-ellipticine (3 mg) was subjected to a paper chromatographic separation (100 γ/cm). Methanol was used to elute material between R_f 0·20 and 0·50 (ellipticine R_f 0·65). After removal of the solvent *in vacuo*, the residue was dissolved in 5 ml of 0·1 N HCl, washed with chloroform, made basic (pH 9) with conc NaOH, and extracted exhaustively with chloroform. The chloroform extracts were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was recrystallized twice from methanol to yield (1 mg) 1,2-dihydro-ellipticine (III) as colorless cubes, m.p. 293–296° (dec.).

This material was identical in infrared and ultraviolet spectra, m.p., mixed m.p. and R_f values with an authentic sample of 1,2-dihydro-ellipticine prepared by dehydrogenation of 1,2,3,4-tetrathydro-ellipticine (VIII).

Isolation of olivacine XIII. A second crude fraction (8 mg) also obtained during the column chromatography of the N-methyl-tetrahydro-ellipticine residues[4] was purified by paper chromatographic separation (130 γ/cm). Material lying between R_f 0·50 and 0·65 was extracted and worked up in the usual manner. The residue crystallized when triturated with methanol. Recrystallization first from isopropyl alcohol and finally from methanol afforded (2 mg) of olivacine (XIII) as yellow cubes, m.p. 317–319° (dec.) (lit.[14] 318–324°); R_f^{BuOH} 0·75, R_q^{BuOH} 1·03.

This material (although paper chromatographic examination indicated that traces of ellipticine

[14] J. Schmutz and F. Hunziker, *Pharm. Acta Helv.* **33**, 341 (1958).

still persisted in the sample) was identical in infrared spectrum, m.p., mixed m.p. and R_f value with an authentic sample of olivacine kindly given to us by Dr. J. Schmutz.

Sodium borohydride reduction of 1,2-*dihydro-ellipticine methonitrate* (IV). An aqueous solution (2 ml) of 60 mg of sodium borohydride was rapidly added to 30 mg of 1,2-dihydro-ellipticine methonitrate dissolved in 7 ml of water. A yellow amorphous solid immediately precipitated. The reaction mixture was shaken for 30 min and then acidified with dil HCl. The acidic aqueous phase was washed with chloroform, made basic (pH 9) with conc NaOH and extracted with ether. The ether extracts were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. Four recrystallizations of the residue afforded (9 mg) N-methyl-tetrahydro-ellipticine[5] as colorless rosettes, m.p. 224·5–225° (lit.[11] 215–218°); R_f^{BuOH} 0·72, R_q^{BuOH} 1·00, R_f^{MEK} 0·23, R_q^{MEK} 1·21; λ_{max}^{MeOH} 340, 327, 317(*sh*), 294, 284(*sh*), 263, 248(*sh*), 242, and 229(*sh*) mμ (log ε 3·56, 3·58, 3·42, 4·26, 3·96, 4·31, 4·57, 4·69 and 4·48 resp.); ν_{max}^{KBr} 1610(16), 1580(48), 1500(35), 1455(14), 1403(34), 1370(15), 1335(21), 1312(14), 1287d(30), 1265(12), 1230(41), 1190(55), 1165(51), 1120t(30), 1075(40), 1012d(54), 983(58), 970(39), 892(43), 820(41), 770(52), 732(10), 705(50).

This material was identical in infrared and ultraviolet spectra, m.p., mixed m.p., and R_f values with an authentic sample of N-methyl-tetrahydro-ellipticine.

Mercuric acetate oxidation of N-*methyl-tetrahydro-ellipticine* (X). N-methyl-tetrahydro-ellipticine (40 mg) was refluxed with 160 mg of mercuric acetate in 3 ml of 5% aqueous acetic acid for 3·5 hr. The initial colorless solution rapidly turned bright yellow in color. After filtration of the mercurous acetate and saturation with hydrogen sulfide the aqueous solution was made strongly acidic with conc HNO_3. The black colloidal precipitate was collected by centrifugation and extracted repeatedly with hot ethanol. On concentration of the ethanol extracts the product crystallized as fine yellow needles. Several recrystallizations from methanol gave (6 mg) 1,2-*dihydro-ellipticine methonitrate* (IV), m.p. 302–307° (dec.).

This material was identical in infrared and ultraviolet spectra, m.p., mixed m.p. and R_f values with the natural salt.

Catalytic reduction of ellipticine (XI). The catalytic reduction of ellipticine appeared to proceed slowly or not at all under a variety of conditions. Reduction over PtO_2 in ethanol, however, could be effected by employing large amounts of catalyst and, although little hydrogen uptake could be detected, the course of the reaction was monitored by observing changes in the ultraviolet spectrum of aliquots withdrawn at regular intervals.

Ellipticine (40 mg) was dissolved in 25 ml of absolute ethanol and hydrogenated over (130 mg) PtO_2 for 12 hr. The colorless reaction mixture was divided into two equal portions. The catalyst was rapidly removed from portion No. 1 by filtration in an atmosphere of nitrogen. Evaporation of the solvent *in vacuo* gave 19 mg of colorless fan shaped crystals which rapidly turned yellow in color on contact with air. Two recrystallizations from methanol afforded (13 mg) 1,2,3,4-*tetrahydro-ellipticine* (VIII), m.p. 160–165° (dec.); R_f^{BuOH} 0.79, R_q^{BuOH} 1·13, R_f^{MEK} 0·30, R_q^{MEK} 1·34; λ_{max}^{MeOH} 341, 327, 316(*sh*), 294, 284(*sh*), 263, 249(*sh*), 242 and 228(*sh*) mμ (log ε values were not obtained, however, the relative extinction coefficients for the absorption maxima were virtually identical to those observed for N-methyl-tetrahydro-ellipticine). As the crystalline material still exhibited great sensitivity toward air, further characterization of the compound was carried out with the acetyl derivative. Portion No. 2 rapidly turned yellow on standing in contact with air and no identifiable products could be isolated after removal of the catalyst.

Acetyl derivative (IX). Acetylation of 1,2,3,4-tetrahydro-ellipticine with acetic anhydride-pyridine followed by several recrystallizations from methanol gave white needles, m.p. 272·5–273°; R_f^{BuOH} 0·86, R_q^{BuOH} 1·23, R_f^{MEK} 0·94, R_q^{MEK} 4·27; λ_{max}^{MeOH} 340, 327, 318(*sh*), 294, 285(*sh*), 263, 248(*sh*), 242 and 229(*sh*) mμ (log ε 3·54, 3·59, 3·45, 4·20, 3·71, 4·30, 4·57, 4·70 and 4·51 resp.); ν_{max}^{KBr} 1630(7), 1612(3), 1492(47), 1455(15), 1420(23), 1361(53), 1338d(62), 1300d(49), 1268(22), 1239(30), 1117(56), 1050(63), 1030d(66), 990d(65), 875(61), 775(58), 740(18). (Found: C, 77·74; H, 6·86; N, 9·61. $C_{19}H_{20}N_2O$ requires: C, 78·04; H, 6·89; N, 9·58%).

Dehydrogenation of 1,2,3,4-*tetrahydro-ellipticine* (VIII). Ellipticine (100 mg) in absolute ethanol (40 ml) was hydrogenated over PtO_2 (154 mg) for 16 hr. After filtration of the catalyst in an atmosphere of nitrogen and removal of the solvent *in vacuo*, the white crystalline product (~70 mg) was immediately dissolved in 70 ml of *o*-dichlorobenzene and rapidly added to a solution of 50 mg of 9,10-phenanthra-quinone in 30 ml of the same solvent. The reaction vessel was quickly flushed with nitrogen, sealed under vacuum and kept at 120–130° for 24 hr. After cooling, the *o*-dichlorobenzene

solution was exhaustively extracted with dil HCl. The acidic aqueous extracts were washed with chloroform, adjusted to (pH 9) with conc NaOH and extracted repeatedly with chloroform. The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was crystallized once from methanol and then subjected to paper chromatographic separation (300 γ/cm). Extraction of the material lying between R_f 0·25 and 0·65 with methanol and removal of the solvent *in vacuo* gave a yellow amorphous residue which was taken up in 10 ml of 0·1 N HCl and washed with chloroform. The acidic aqueous phase was made basic (pH 10) and extracted with chloroform. The chloroform extracts were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue (26 mg) crystallized on trituration with methanol. Elution with chloroform from "Woelm" almost neutral, activity 1, alumina and three recrystallizations from methanol gave (12 mg) of 1,2-*dihydro-ellipticine* (III), m.p. 296–300° (dec.); R_f^{BuOH} 0·73, R_q^{BuOH} 1·05, R_f^{MEK} 0·34, R_q^{MEK} 1·50; $\lambda_{max}^{0\cdot1\,N\,HCl}$ 378, 312, 301, 279, 270(sh), and 235 mμ (log ε 4·36, 4·28, 4·15, 4·62, 4·45 and 4·42 resp.); ν_{max}^{KBr} 1615(14), 1595(14), 1570(10), 1495(17), 1445(29), 1410(38), 1355(35), 1325(7), 1265(20), 1225(31), 1167(45), 1123(41), 1028(42), 930d(64), 909(43), 843(50), 775(40), 750(10), 660(44). (Found: C, 82·12; H, 6·42; N, 11·36. $C_{17}H_{16}N_2$ requires: C, 82·23; H, 6·49; N, 11·28%).

This material was identical in infrared and ultraviolet spectra, m.p., mixed m.p. and R_f values with the natural base.

Conversion of 1,2-*dihydro-ellipticine* (III) *to* 1,2-*dihydro-ellipticine methochloride* (IV). Natural 1,2-dihydro-ellipticine (20 mg) in acetone (30 ml) was rapidly mixed with methyl iodide (5 ml) in acetone (5 ml) and left at room temperature for 1 hr. The bright yellow crystalline precipitate (29 mg) was filtered, washed with acetone and dissolved in methanol–water 1 : 1 (40 ml). The aqueous-methanolic solution of 1,2-dihydro-ellipticine methiodide was passed over Dowex-1 (2 g) in the chloride form. Removal of the solvent *in vacuo* gave 15 mg of a yellow crystalline residue a portion of which was chromatographed on paper (165 γ/cm). Extraction with methanol of material lying between R_f 0·18 and 0·30, evaporation of the solvent under reduced pressure, and two recrystallizations from methanol-ethyl acetate afforded (7 mg) of 1,2-*dihydro-ellipticine methochloride* (VII), m.p. 296–306° (dec.); R_f^{MEK} 0·185, R_q^{MEK} 1·16; λ_{max}^{MeOH} 383, 314, 302, 282, 271(*sh*), and 236 mμ (log ε 4·40, 4·20, 4·02, 4·62, 4·40 and 4·34 resp.); ν_{max}^{KBr} 1650(29), 1595(30), 1575(21), 1500(59), 1447(48), 1412(49), 1375(49), 1331(21), 1305(50), 1250(45), 1215(45), 1188(52), 1170(57), 1110(64), 778(55), 749(42).

This material was identical in infrared and ultraviolet spectra, m.p., mixed m.p. and R_f value with an authentic sample of 1,2-dihydro-ellipticine methochloride (VII) prepared from 1,2-dihydro-ellipticine methonitrate (IV) by ion exchange with Dowex-1 (chloride form).

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LYCOPODIUM ALKALOIDS—V

THE STRUCTURE AND STEREOCHEMISTRY OF FAWCETTIINE, CLAVOLONINE AND RELATED ALKALOIDS

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Abstract—Fawcettiine, clavolonine and annofoline have been interrelated and their stereochemistries elucidated. The conversion of clavolonine to lycopodane, the Wolff–Kishner reduction product of lycopodine is described and a structure is proposed for an abnormal Hofmann degradation product of clavolonine.

FAWCETTIINE, $C_{18}H_{29}NO_3$ the major alkaloid of *L. fawcettii*[1] and a minor component of *L. annotinum*[2,3] and Jamaican *L. clavatum*[4] has been shown to be a tetracyclic tertiary base possessing a hydroxyl group and an O-acetyl residue. Mild hydrolysis of the alkaloid affords deacetylfawcettiine, $C_{16}H_{27}NO_2$ which is also naturally occurring in Jamaican *L. clavatum*.[3] Acetylation of deacetylfawcettiine or fawcettiine gives rise to the diacetate Base K, $C_{20}H_{31}NO_4$ found naturally in L. fawcettii.[3]

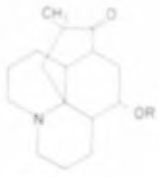
From the chromium trioxide oxidation of fawcettiine, a ketoacetate dehydrofawcettiine, $C_{18}H_{27}NO_3$ was isolated which hydrolysed readily in base to a compound $C_{16}H_{25}NO_2$. The infra-red spectrum of the latter in Nujol bore a strong resemblance to that of annofoline[2] but was clearly not identical and the melting points were also different. However, the infra-red spectrum in chloroform solution was identical to that of annofoline in this solvent and the optical rotation ($[\alpha]_D$ −132°) was in good agreement with the published value for annofoline ($[\alpha]_D$ −131°).[2] Subsequently, it was found that crystallization from a concentrated ethereal solution gave material showing an infra-red spectrum in Nujol identical to that published for annofoline.* When the methiodide of the hydrolysis product was compared with that of annofoline the two were shown to be identical (melting and mixed melting points and infra-red curves). More recently[5] Anet and Khan have shown annofoline to have the structure (III) so that dehydrofawcettiine must be (II) and fawcettiine (I). Deacetylfawcettiine and Base K must be (IV) and (V) respectively. In an effort to corroborate the identity of annofoline and deacetyldehydrofawcettiine, annofoline acetate was prepared but its methiodide (m.p. 289–290° $[\alpha]_D$ −66°) was found to be different from dehydrofawcettiine methiodide (m.p. 271–272° $[\alpha]_D$ −48°). Since annofoline can be reduced to deacetylfawcettiine,[5] the difference between annofoline acetate and dehydrofawcettiine must be stereochemical rather than skeletal (see later).

* The melting point (and the infra-red spectrum in Nujol) of annofoline are somewhat variable. Dr. Anet (Private communication) has also observed this phenomenon, which is presumably dependent on the equilibrium between the hemi-ketal and hydroxy-ketone forms of this base (see ref. 5).

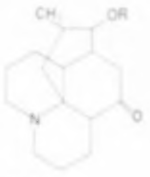
[1] R. H. Burnell, *J. Chem. Soc.* 3091 (1959).
[2] F. A. L. Anet and N. H. Khan, *Canad. J. Chem.* **37**, 1589 (1959).
[3] R. H. Burnell, B. S. Mootoo and D. R. Taylor, *Canad. J. Chem.* **38**, 1927 (1960).
[4] R. H. Burnell and B. S. Mootoo, *Canad. J. Chem.* In press (1961).
[5] F. A. L. Anet and N. H. Khan, *Chem. & Ind.* 1238 (1960).

Clavolonine, $C_{16}H_{25}NO_2$ was obtained as a major component of Jamaican *L. clavatum*,[4] and is also a tetracyclic tertiary base which from the infra-red spectrum contains a hydroxyl and a carbonyl in a six-membered (or larger) ring. Oxidation of clavolonine with chromium trioxide–pyridine gave a diketone, $C_{16}H_{23}NO_2$, characterized as the methiodide, m.p. 310–312° which was identical to the methiodide of the diketone obtained (albeit in low yield) by the similar oxidation of deacetylfawcettiine (IV). This ketone could have arisen from a compound epimeric to annofoline or from either epimer corresponding to VI. Of these, the latter seemed the more likely since clavolonine shows a peak at 1410 cm^{-1} in the infra-red, suggestive of a methylene grouping adjacent to the carbonyl. The following conversion of deacetylfawcettiine to clavolonine clearly distinguishes between these possibilities.

I R=CH$_3$CO, R'=H
IV R=R'=H
V R=R'=CH$_3$CO
VII R=H, R'=CH$_3$CO



II R=CH$_3$CO
III R=H



VI R=H
VIII R=CH$_3$CO

IX R=OH
X R=Cl

XI R=OH
XIII R=H

XII

Acetylation of deacetylfawcettiine in acetic anhydride–pyridine at room temperature (or using the acetic anhydride–sodium acetate method) affords Base K but if the reaction is carried out at 5° a new monoacetate, isofawcettiine is produced which may be further acetylated to Base K or hydrolysed back to deacetylfawcettiine. Isofawcettiine (which must be VII) was oxidized to the corresponding ketone VIII, dehydroisofawcettiine, hydrolysis of which gave a substance identical in every respect to clavolonine. This shows the latter to be VI and (unlike annofoline) the O-acetyl derivative of clavolonine was shown to be identical to dehydroisofawcettiine. Reduction of clavolonine with an ethereal solution of lithium aluminium hydride afforded (as the only product) deacetylfawcettiine (IV), whereas lithium in liquid ammonia[6] or sodium in isobutanol gave the epimeric α-dihydroclavolonine, m.p. 263–266°.

Deacetylfawcettiine is readily dehydrated by thionyl chloride in benzene to give an unsaturated alcohol, anhydrodeacetylfawcettiine, $C_{16}H_{25}NO^1$. The NMR trace of the latter shows that the double bond bears only one proton (τ, 4·45) and also that the grouping CH_3—C—H is preserved (τ, 9·00; J 5·9 cps) so that the anhydro product is IX. This is contrary to our findings[3] that fawcettiine can be dehydrated and then

[6] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **75**, 1282 (1953).

hydrolysed to anhydrodeacetylfawcettiine but one must assume that in the work-up from the phosphorus pentoxide dehydration both hydrolysis and acid catalysed elimination must have occurred. Confirmation of structure (IX) for anhydrodeacetylfawcettiine was obtained by the ready elimination of water from isofawcettiine (thionyl chloride in benzene) followed by hydrolysis to IX. The best method for the preparation of IX was found to be treatment of deacetylfawcettiine with ethyl chloroformate to give the mono-ester, followed by thionyl chloride dehydration and then hydrolysis. The anhydro compound obtained from deacetylfawcettiine directly was accompanied by smaller amounts of an unsaturated chlorine containing substance, $C_{16}H_{24}NCl$ for which we tentatively propose the structure (X). Prolonged refluxing of anhydrodeacetylfawcettiine in a benzene solution of thionyl chloride also produced the same chloro compound.

A comparison of the optical rotations of a series of compounds obtainable from lycopodine and a similar series from clavolonine (see Fig. 1) led us to believe clavolonine to be a hydroxy lycopodine and the stereochemistry of the ring systems of the two alkaloids to be the same. The rotations of the corresponding methiodides reflect the same relationship.

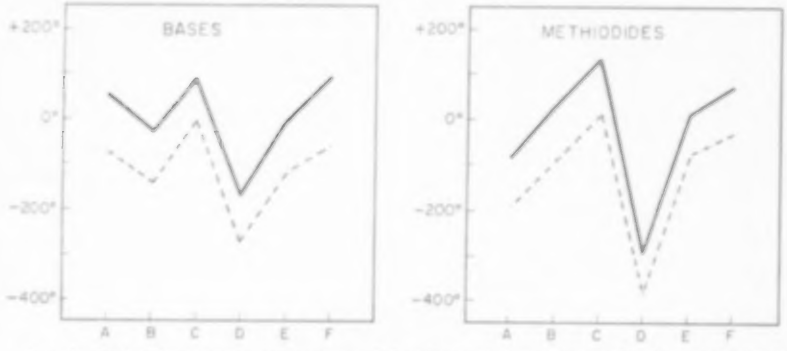


FIG. 1. Molecular rotation comparison of clavolonine (—) and lycopodine (— —) derivatives. A: ketone; B: lithium aluminium hydride reduction product; C: sodium in alcohol reduction product; D: anhydro compound (dehydration of B with thionyl chloride); E: acetate (acetic anhydride–pyridine treatment of B); F: Wolff–Kishner reduction product.

This similarity of the two bases was confirmed as follows: Wolff–Kishner reduction of clavolonine (VI) afforded the dihydrodeoxyclavolonine (XI) which was smoothly oxidized to the corresponding ketone (XII). The latter was again subjected to Wolff–Kishner reduction and the product, a mobile oil characterized as the methiodide, m.p. 284–286°. The infra-red spectrum of this derivative was indistinguishable from that of the corresponding derivative of lycopodane (XIII), obtained from lycopodine and a mixed melting point of the methiodides showed no depression. In our hands, lycopodine when subjected to the same conditions as used for the Wolff–Kishner reduction of clavolonine, yielded only the hydrazone, previously reported by Marion[7a] but Ayer[7b] and co-workers have been able to effect the reduction in one step. However we found lycopodine hydrazone to be converted smoothly to lycopodane by heating

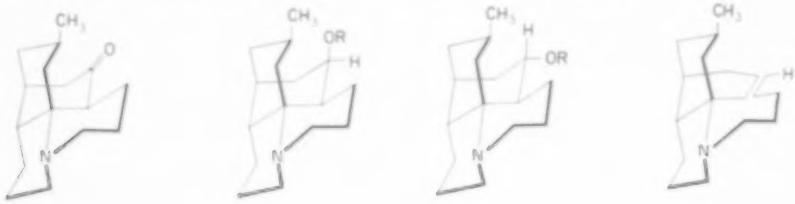
[7a] D. B. MacLean, R. H. F. Manske and L. Marion, *Canad. J. Res.* **28B**, 460 (1950); [b] W. A. Ayer and G. G. Iverach, Personal communication.

in a sealed tube at 190–195° with ethanolic sodium ethoxide. The ketone (XII) can be reduced to dihydrodeoxyclavolonine (XI) in high yield by sodium in diethylene glycol.

Wolff–Kishner reduction of dehydrofawcettiine afforded, as the only product a compound, $C_{16}H_{27}NO$, which is isomeric but not identical to dihydrolycopodine (XVa). Anet[8] has also described this reduction product and has suggested the structure (XXII) (CH_2 for C:O) since it is also obtained by similar reduction of annofoline.

It was hoped to correlate clavolonine and lycopodine by reducing both with red phosphorus in hydriodic acid but the only tractable product from clavolonine analysed for $C_{16}H_{25}NI_2$ and normal methods for the removal of iodine have so far proved ineffective.

From MacLean's work on lycopodine,[9] the stereochemistry of the molecule is readily deduced to be XIV which accounts for the hindered nature of the carbonyl and the internal cyclization of α-cyanobromolycopodine. The dihydrolycopodine (m.p. 168°) (XVa) obtainable by the lithium aluminium hydride reduction of lycopodine undoubtedly has the hydroxyl group axial since elimination proceeds readily in benzene containing thionyl chloride at room temperature to give anhydrodihydrolycopodine (XVII). When sodium in isobutanol is used for the reduction, the epimeric α-dihydrolycopodine (XVIa) is produced which is not readily dehydrated but does form a cathylate with ethyl chloroformate in pyridine.[10] Dihydrolycopodine (XVa) does not react with the latter even after 24 hr. The infra-red spectra of the acetyl derivatives (chloroform solution) are in agreement with this since XVb shows a split acetate whereas XVIb shows only a single peak in the 1250 cm^{-1} region.[11]

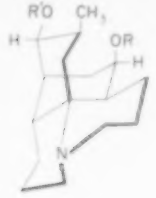


XIV XV a R=H b R=CH_3CO XVI a R=H b R=CH_3CO XVII

Clavolonine is reduced by lithium aluminium hydride in ether to deacetylfawcettiine and by sodium in isobutanol to α-dihydroclavolonine, these reactions are analogous to the respective reductions of lycopodine. Clavolonine affords an acetate (single acetate peak) and forms a cathylate with ethyl chloroformate. Dehydration is not accomplished with thionyl chloride nor even by phosphorus pentoxide in boiling toluene. The facile dehydration of IV to anhydrodeacetylfawcettiine shows the hydroxyl at C_7 to be *axial* and *trans* to the C_8 hydrogen atom. Since IV, which reacts with ethyl chloroformate at one of the hydroxyl groups only, forms the monoacetate (VII) (single acetate peak) which is unaffected by ethyl chloroformate in pyridine then the readily acetylated hydroxyl group is equatorially disposed to the bridge ring. Fawcettiine (I) reacts readily with ethyl chloroformate and shows a complex acetate peak in the infra-red.

[8] F. A. L. Anet, *Tetrahedron Letters* No. 20, 13 (1960).
[9] W. A. Harrison and D. B. MacLean, *Chem. & Ind.* 261 (1960).
[10] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Utne, *J. Amer. Chem. Soc.* **74**, 3309 (1952).
[11] H. Hirschmann, *J. Amer. Chem. Soc.* **74**, 5357 (1952).

Thus, this group of bases is accommodated satisfactorily by XVIIIa–d, anhydrodeacetylfawcettiine by XIX and clavolonine by XX.



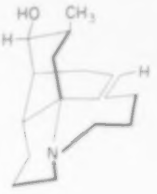
XVIII

a R=R'=H
Deacetylfawcettiine

b R=CH$_3$CO, R'=H
Fawcettiine

c R=H, R'=CH$_3$CO
Isofawcettiine

d R=R'=CH$_3$CO
Base K



XIX

XX

From the infra-red spectrum of clavolonine in chloroform solution and in particular its resemblance to that of annofoline, it was thought[12] that both of these bases existed as equilibria between hydroxy-ketone and hemiketal forms but quantitative infra-red comparison spectra in chloroform (Fig. 2) show that the hemi-ketal form of clavolonine makes a very small contribution, if indeed it is present at all.

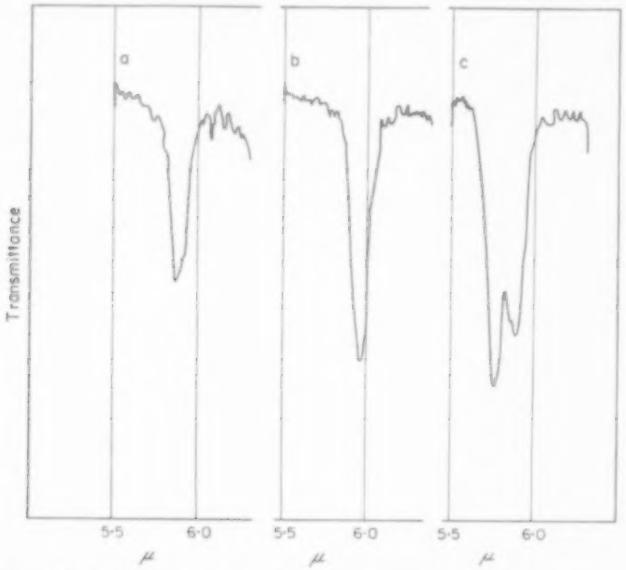


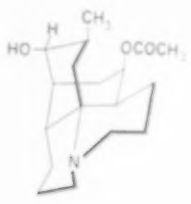
FIG. 2. Comparison of the intensities of the carbonyl absorption in the infra-red spectra of (a) annofoline (b) clavolonine and (c) acetyl clavolonine. The concentration of the base is 20 mg/ml in each case (chloroform solution).

Lofoline,[2] which has been shown to be epimeric to fawcettiine[8] and thus XXI, dehydrates readily as would be expected of a compound containing an *axial* hydroxyl group with an adjacent *trans* hydrogen substituent. Lofoline does not form a cathylate.

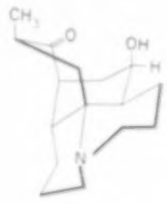
Optical rotatory dispersion measurements on clavolonine and lycopodine show that both exhibit positive Cotton effects. Applying Djerassi's Octant Rule[13] to these

[12] R. H. Burnell and D. R. Taylor, *Chem. & Ind.* 1239 (1960).
[13] C. Djerassi, *Optical Rotatory Dispersion* p. 178. McGraw-Hill, New York (1960).

findings suggests the absolute stereochemistry of these bases to be as shown (XX and XIV) rather than the mirror-image representations which have been used in previous publications.* Negative Cotton effects are shown by dehydrofawcettiine (II) and the ketone (XII) in agreement with the proposed absolute stereochemistry. Annofoline, which necessarily contains the bridge ring in the boat form since this base exists in both the hemi-ketal and hydroxy-ketone forms, also shows a negative Cotton effect and must clearly be XXII. The change of ring conformation (from the chair form in fawcettiine and dehydrofawcettiine) must involve inversion of the configuration of



XXI



XXII

XXIII

the adjacent methyl grouping, since an *axial* (flag-pole) methyl group alpha to the carbonyl would produce a positive Cotton effect. The stereochemical difference between annofoline acetate and dehydrofawcettiine referred to earlier, must arise during the basic hydrolysis of the latter. Under these conditions the hemi-ketal form of annofoline is greatly favoured and this explains why annofoline is the only product from the hydrolysis. The acetylation of annofoline is considerably more complex if carried out in the presence of added bases such as pyridine or sodium acetate but refluxing in acetic anhydride alone affords annofoline acetate in high yield.

Lycopodium alkaloids in general, have shown no great susceptibility to Hofmann degradation. Refluxing clavolonine methiodide in tertiary butanol containing potassium t-butoxide afforded a crystalline product, $C_{17}H_{27}NO_2$ m.p. 196–198° which contained one N-methyl group (analysis), a carbonyl and a hydroxyl (infra-red). The NMR spectrum, showed no bands at low field ascribable to olefinic protons and the infra-red spectrum contained no peaks characteristic of a terminal methylene grouping. Since the product contains an N-methyl grouping, fission of either the C_1—N or the C_{12}—N bonds must have occurred but the potential propene side-chain must have cyclized intramolecularly. Both clavolonine and the Hofmann base show infra-red peaks at 1410 cm^{-1} which suggests the presence of the grouping —CH_2C:O—. This band does not appear in the infra-red spectrum of the lithium aluminium hydride reduction product obtained from the Hofmann product nor in deacetylfawcettiine (the reduction product from clavolonine). Complete reduction of the carbonyl grouping of the Hofmann base by this method requires considerably longer refluxing than the reduction of clavolonine, suggesting a greater degree of hindrance to the approaching reagent. The optical rotatory dispersion of the Hofmann product shows a negative Cotton effect, as opposed to the positive effect in clavolonine, indicating the introduction of an axially disposed substituent adjacent to the carbonyl group. This evidence is consistent with the structure (XXIII) for the Hofmann base.

* Dr. Z. Valenta has informed us that the University of New Brunswick workers have deduced this same absolute stereochemistry.

EXPERIMENTAL

The infra-red figures were measured as Nujol mulls unless otherwise stated and the pK titrations were performed in 50% aqueous MeOH. Melting points are uncorrected and the optical rotations were measured at 28–30°.

Dehydrofawcettiine (II)

A solution of fawcettiine (2·4 g) in pyridine (30 ml) was added slowly to a slurry of chromium trioxide (4 g) in pyridine (40 ml) while the temperature was maintained below 20°. The mixture was stirred at room temperature for 9 hr and then made basic with ammonia and extracted with chloroform. The crude product obtained by evaporation of the latter (2·24 g) was run over alumina in benzene affording solid dehydrofawcettiine (1·6 g) and on further elution unchanged fawcettiine (0·41 g). The dehydrofawcettiine was recrystallized from acetone, m.p. 139–140°, $[\alpha]_D$ −68° (*c* 1·12, EtOH), I.R. 1740 and 1240, 1225 (acetate) 1710 (C:O) cm^{-1}. R.D. in EtOH (*c* 0·045) 25°; $[\alpha]_{700}$ −51°, $[\alpha]_{589}$ −84°, $[\alpha]_{315}$ −1000°, $[\alpha]_{295}$ −194°). Found: C, 71·0; H, 9·4; O, 15·5; N, 4·5. $C_{18}H_{27}NO_3$ requires: C, 70·8; H, 8·9; O, 15·7; N, 4·6%).

The methiodide, m.p. 271–272° (inserted at 250°), $[\alpha]_D$ −48° (*c* 1·49, 50% EtOH). (Found: C, 51·2; H, 6·8; N, 3·1; I, 28·6. $C_{18}H_{27}NO_3.CH_3I$ requires: C, 51·0; H, 6·8; N, 3·1; I, 28·4%).

Annofoline (*by hydrolysis of* II)

To dehydrofawcettiine (1·37 g) in MeOH was added a solution of sodium hydroxide (10 g) in MeOH (25 ml) and water (45 ml). After 16 hr at room temperature, the turbid solution was diluted with water and extracted with chloroform. Concentration gave an oil (1·2 g) which solidified on standing. The annofoline, after recrystallization from ether had m.p. 150–151°, $[\alpha]_D$ −132° (*c* 1·05, EtOH), I.R. 3450 (OH) and 1704 (C:O) cm^{-1}. The infra-red spectra in Nujol and in chloroform were identical to those of annofoline. R.D. in EtOH (*c* 0·2) 24°; $[\alpha]_{700}$ −94·5, $[\alpha]_{589}$ −130·5°, $[\alpha]_{305}$ −1135°, $[\alpha]_{295}$ −905°.

The methiodide, from MeOH–acetone, m.p. 308–310° (inserted at 240°). (Found: C, 50·0; H, 7·0; N, 3·6; I, 31·8. $C_{16}H_{25}NO_4.CH_3I$ requires: C, 50·4; H, 7·0; N, 3·5; I, 31·3%).

Annofoline acetate methiodide

Annofoline (100 mg) was refluxed for 5 hr in acetic anhydride. After removing the solvent *in vacuo* the residue was dissolved in benzene and run through a short alumina column. The eluate, which showed only one spot on paper, was converted to the methiodide, m.p. 289–290° (inserted at 250°), $[\alpha]_D$ −66° (*c* 1·31, 50% EtOH). (Found: C, 50·9; H, 6·9; N, 2·9. $C_{18}H_{27}NO_4.CH_3I$ requires: C, 51·0; H, 6·8; N, 3·1%).

Dehydroclavolonine

(a) *From deacetylfawcettiine*. Deacetylfawcettiine (795 mg) was dissolved in pyridine (7·5 ml) and the solution added to pyridine (15 ml) containing chromium trioxide (1·5 g), the temperature being kept at 20°. The mixture was stirred at room temperature for 2 hr, then poured into water, made strongly basic with sodium hydroxide and chloroform extracted. Evaporation gave the crude base (570 mg) which was run over alumina in benzene to give the dione (140 mg) as an oil. Further elution afforded unreacted deacetylfawcettiine (270 mg). The dione readily formed the methiodide, m.p. 310–312° (decomp., inserted at 250°) identical in every respect to that obtained in (b).

(b) *From clavolonine*. Clavolonine (2·27 mg) was oxidised as in (a) yielding largely unchanged starting material (1·5 g) and the dione (0·41 g). The methiodide, m.p. 310·312° (decomp., inserted at 250°), showed absorption in the I.R. at 1725 and 1707 (C:O) cm^{-1}. (Found: C, 50·2; H, 6·6; N, 3·6; O, 8·2; I, 31·6; N–Me, 3·8. $C_{16}H_{23}NO_4.CH_3I$ requires: C, 50·6; H, 6·5; N, 3·5; O, 7·9; I, 31·5; N–Me, 3·7%).

Acetylation of deacetylfawcettiine

(a) *At room temperature*. Deacetylfawcettiine (377 mg) was dissolved in pyridine and acetic anhydride added. After 16 hr at room temperature the solution was evaporated to dryness and the oil (410 mg) run over alumina in benzene. The first eluate (60 mg) was shown by its melting point, 113–117°, mixed melting point and infra-red spectrum to be Base K, V. Further benzene elution gave a white crystalline solid (240 mg) which was a mixture of Base K and isofawcettiine (VII) (102 mg),

separated by fractional sublimation. The latter was sublimed for analysis, m.p. 207–208°, $[\alpha]_D$ +48° (*c* 0·87, EtOH). I.R. 3100 (OH) and 1724, 1235 (acetate) cm^{-1}. I.R. in carbon tetrachloride 3100, 1726 and 1240 (sharp single band) cm^{-1}. (Found C, 70·5; H, 9·5; O, 15·6; O–Ac, 14·3. $C_{16}H_{29}NO_3$ requires: C, 70·3; H, 9·5; O, 15·6; O–Ac, 14·9%).

The methiodide, m.p. 288–289° was prepared in acetone. (Found C, 50·7; H, 7·5; I, 28·5. $C_{16}H_{29}NO_3.CH_3I$ requires: C, 50·8; H, 7·2; I, 28·2%.)

(b) *At low temperature*. Deacetylfawcettiine (1·23 g) was acetylated as above but the temperature was kept at 5° for 20 hr. The crude oil obtained showed only one spot on paper chromatography and after running over alumina, gave an almost quantitative yield of isofawcettiine (1·35 g).

Hydrolysis of VII (20 mg) in MeOH (1 ml) and water (1 ml) containing sodium hydroxide (0·5 g) gave deacetylfawcettiine, m.p. 205–207° (mixed m.p. and infra-red).

Dehydroisofawcettiine (VIII)

Isofawcettiine (0·67 g) was oxidized with chromium trioxide (1·5 g) in pyridine as described above. The crude product (0·5 g) was purified by alumina chromatography affording a colourless oil (0·4 g), I.R. in chloroform, 1724 and 1245 (sharp single peak–acetate), 1698 (C:O) cm^{-1}, characterized by conversion to the methiodide, m.p. 308° (inserted at 250°). (Found: C, 50·6; H, 7·0; N, 3·2; O, 11·4; I, 28·2. $C_{16}H_{27}NO_3.CH_3I$ requires: C, 51·0; H, 6·8; N, 3·1; O, 11·7; I, 28·4%).

Hydrolysis of VIII *to clavolonine* (VI)

Dehydroisofawcettiine (200 mg) was dissolved in MeOH (10 ml) and a solution of sodium hydroxide (5 g) in water (10 ml) was added. After 4 hr the mixture was diluted with water and chloroform extracted to yield a white solid (160 mg) which after sublimation had m.p. 234–235° (unchanged on admixture with clavolonine). R.D. in EtOH (*c* 0·05) 25°; $[\alpha]_{650}$ +40°, $[\alpha]_{310}$ +2440°, $[\alpha]_{300}$ +1310°. The infra-red traces in nujol and chloroform were identical to those of clavolonine.

Clavolonine acetate methiodide Clavolonine (100 mg) was acetylated in acetic anhydride–pyridine at room temperature for 18 hr. The crude acetate (140 mg) was purified by alumina chromatography affording an oil (125 mg) showing an identical infra-red spectrum to dehydroisofawcettiine (chloroform solution). The methiodide, m.p. 308° (decomp.) was not depressed on admixture with dehydroisofawcettiine methiodide of the same melting point.

Reduction of clavolonine

(a) *With lithium aluminium hydride*. To clavolonine (195 mg) in anhydrous ether was added excess lithium aluminium hydride and the mixture refluxed for 16 hr. Wet MeOH was used to decompose the unreacted hydride and after filtration, the solution was taken to dryness and triturated with acetone. Evaporation of the filtered acetone solution gave white crystals, m.p. 206–207°, $[\alpha]_D$ −6° (*c* 1·0 EtOH) after sublimation (180 mg). Paper chromatography, infra-red comparison and mixed m.p. showed this material to be deacetylfawcettiine.

The methiodide (not previously described), m.p. 289–290° (decomp.), $[\alpha]_D$ −1·5° (*c* 1·37 50% EtOH). (Found: C, 50·1; H, 7·6; I, 31·3. $C_{16}H_{27}NO_2.CH_3I$ requires: C, 50·1; H, 7·4; I, 31·2%).

Sodium borohydride in methanol gave the same product but the reaction was complete only after refluxing for 3 hr.

(b) *With sodium in isobutanol*. Clavolonine (500 mg) was dissolved in dry toluene (60 ml) and anhydrous isobutanol (0·75 ml) added. This solution was added to a suspension of sodium (100 mg) in toluene (3 ml) and the mixture stirred overnight. Water was added and the toluene layer taken to dryness to give an oil (200 mg) which was run over alumina in benzene. Some unchanged clavolonine (15 mg) was first eluted in chloroform and subsequent elution with MeOH afforded α-dihydroclavolonine (70 mg), m.p. 263–266°, $[\alpha]_D$ +33° (*c* 1·01 EtOH). I.R. 3370 and 3100 (*sh*) cm^{-1}. A sample was sublimed for analysis. (Found: C, 72·7; H, 10·4; O, 12·6. $C_{16}H_{29}NO_2$ requires: C, 72·4; H, 10·3; O, 12·1%).

Reduction of clavolonine by lithium in liquid ammonia gave the same α-dihydroclavolonine but in low yield.

Anhydrodeacetylfawcettiine (IX)

(a) *From isofawcettiine*. Isofawcettiine (100 mg) was dissolved in benzene and excess thionyl chloride added. After 4 hr the solution was evaporated to dryness and the residue taken up in water, basified with ammonia and chloroform extracted. The brown oil (100 mg) was purified by alumina

chromatography, giving anhydroisofawcettiine (80 mg) as a colourless oil. A portion of the material was converted to the methiodide, m.p. 258–261°, identical with acetylanhydrodeacetylfawcettiine methiodide (see later).

The bulk of the material (50 mg) was hydrolysed at room temperature in methanolic sodium hydroxide affording IX (40 mg).

(b) *From deacetylfawcettiine.* IV (700 mg) was dissolved in pyridine and excess ethyl chloroformate added. After 6 hr at room temperature the solution was taken to dryness *in vacuo* and the residue suspended in water, basified with ammonia and extracted with chloroform. The crude ester was run over alumina in benzene and a small part sublimed for analysis, m.p. 195–196°, I.R. 3100 (*sh.* OH), 1737 and 1258 (ester) cm^{-1}. (Found: C, 67·4; H, 9·3; O, 19·1; O–Et, 13·5. $C_{19}H_{31}NO_4$ requires: C, 67·6; H, 9·3; O, 19·0; O–Et, 13·4%).

The remaining ester was treated with excess thionyl chloride in benzene at room temperature for 4 hr and the unsaturated ester obtained by evaporation and extraction. After hydrolysis in methanolic sodium hydroxide at room temperature the crude product was run over alumina in benzene giving first an unidentified oil (80 mg) and then the anhydrodeacetylfawcettiine IX (550 mg) as a white solid, m.p. somewhat variable but ca. 75–85°, $[\alpha]_D$ −70° (*c* 1·18 EtOH). (Found: C, 77·6; H, 10·1; N, 5·4; O, 6·8; pK, 9·7. $C_{16}H_{25}NO$ requires: C, 77·7; H, 10·2; N, 5·7; O, 6·5%).

The methiodide, m.p. 263–265° (from MeOH). (Found: C, 52·5; H, 7·5; N, 3·9; I, 32·6. $C_{16}H_{25}NO.CH_3I$ requires: C, 52·5; H, 7·3; N, 3·6; I, 32·6%).

Acetylation of anhydrodeacetylfawcettiine

Treatment of IX (50 mg) with pyridine (4 ml) and acetic anhydride at room temperature for 20 hr gave an oil showing acetate peaks at 1730 and 1250 cm^{-1} in the infra-red (chloroform solution) which was run over alumina and converted to the methiodide, m.p. 258–261°. (Found: C, 52·7; H, 7·1; O, 7·6; I, 29·2; O–Ac, 10·3. $C_{18}H_{27}NO_2.CH_3I$ requires: C, 52·9; H, 7·0; O, 7·4; I, 29·4; O–Ac, 10·0%).

Chlorodeoxyanhydrodeacetylfawcettiine (X)

After room temperature treatment of IV (704 mg) with thionyl chloride in benzene for 6 hr and evaporation of the volatile constituents, the residue was taken up in water, basified with ammonia and extracted with chloroform. The crude base (680 mg) was chromatographed in benzene over alumina affording first an intractable oil (30 mg) and then a solid (70 mg) showing no hydroxyl band in the infra-red. A sublimed sample had m.p. 126–128°, $[\alpha]_D$ −130° (*c* 1·04 EtOH). (Found: C, 72·4; H, 9·4; O, 0·0; Cl, 13·5. $C_{16}H_{24}NCl$ requires: C, 72·3; H, 9·1; O, 0·0; Cl, 13·3%).

Further elution of the column gave IX (500 mg). Room temperature treatment of IX with thionyl chloride in benzene for 12 hr produced only very small amounts of the chloro compound (X) but treating IX (130 mg) with the same reagents under reflux for 16 hr gave, after chromatography mainly X (87 mg).

Anhydrolofoline

Lofoline dehydrated readily in thionyl chloride and the product, obtained as described previously, converted to the methiodide, m.p. 261–264° (decomp.). I.R. 1728, 1253 and 1238 (acetate) cm^{-1}. (Found: C, 53·1; H, 7·0; N, 2·9. $C_{19}H_{27}NO_2.CH_3I$ requires: C, 52·9; H, 7·0; N, 3·2%).

Wolff–Kishner reduction of clavolonine

Sodium (0·4 g) in diethylene glycol was heated to 180° and anhydrous hydrazine distilled into the solution until it refluxed freely at 180°. Clavolonine (0·9 g) was added to the cooled solution which was then refluxed for 16 hr. Excess hydrazine was distilled from the reaction flask until the liquid temperature reached 215–220° and refluxing continued for 24 hr. The cooled solution was diluted with water and chloroform extracted. The chloroform was washed with water, dried over sodium sulphate and evaporated to give the solid dihydrodeoxyclavolonine (XI) (0·66 g) which was recrystallized from acetone, m.p. 164–167° and then sublimed for analysis, $[\alpha]_D$ +14° (*c* 1·73 EtOH). I.R. 3380 and 3070 (OH and bonded OH) cm^{-1}. (Found: C, 77·0; H, 10·8; N, 5·9; O, 6·7. $C_{16}H_{27}NO$ requires: C, 77·1; H, 10·9; N, 5·6; O, 6·7%).

Lycopodane (XIII)

(a) *From dihydrodeoxyclavolonine.* The base (XI) (0·66 g) in pyridine (10 ml) was added to a cold slurry of chromium trioxide (3·3 g) in pyridine (15 ml) and the oxidation continued with occasional

shaking for 6 hr at room temperature. The product (0·4 g) was obtained in the usual manner and purified over a short alumina column. The ketone (XII) (350 mg) showed I.R. absorption at 1707 (C:O) cm^{-1}. R.D. of a sublimed sample, in EtOH (*c* 0·057) 25°; $[\alpha]_{589}$ −211°, $[\alpha]_{317}$ −1320°, $[\alpha]_{310}$ −1250°.

The ketone (270 mg) was subjected to the Wolff–Kishner reduction as described above, affording (after alumina chromatography) a colourless oil (XIII) (150 mg), $[\alpha]_D$ −31·5° (*c* 0·92 EtOH), showing neither carbonyl nor hydroxyl peaks in the infra-red. For characterization, the methiodide was prepared, m.p. 287°, $[\alpha]_D$ −20° (*c* 0·86 EtOH). (Found: C, 54·6; H, 8·2; N, 3·7; I, 34·0. Calc. for $C_{16}H_{27}N.CH_3I$: C, 54·4; H, 8·1; N, 3·7; I, 33·8%).

Mixed melting points with lycopodane methiodide obtained from lycopodine hydrazone, and a sample of lycopodane methiodide from Dr. W. A. Ayer gave no depression and the infra-red spectra were identical.

During the Wolff–Kishner reduction, a colourless oil (30 mg) distilled from the reaction flask with the excess hydrazine. Paper chromatography showed this to be lycopodane and it formed the same methiodide as described above.

(b) *From lycopodine*. Wolff–Kishner reduction of lycopodine (250 mg), employing the conditions described for clavolonine, gave a crude product (235 mg) showing a strong band at 1635 (C:N) cm^{-1} in the infra-red (chloroform solution) which was presumably lycopodine hydrazone. The latter (110 mg) was dissolved in excess ethanolic sodium ethoxide and heated in a sealed tube at 190–195° for 12 hr. After dilution and extraction, the oily product was sublimed and the volatile sublimate (XIII) (100° at 0·2 mm) converted to the methiodide, m.p. 286–287°, which showed no depression in melting point when mixed with the methiodide from (a).

Wolff–Kishner reduction of dehydrofawcettiine

Dehydrofawcettiine (370 mg) was reduced as described above and the crude dihydrodeoxyannofoline (280 mg) recrystallised from acetone, m.p. 194–195°, $[\alpha]_D$ −34·5° (*c* 0·87 EtOH), I.R. 3220 (OH) cm^{-1}. (Found: C, 77·4; H, 10·3; O, 6·9; pK 9·9. $C_{16}H_{27}NO$ requires: C, 77·1; H, 10·9; O, 6·4%).

Reduction of clavolonine (red phosphorus and hydriodic acid)

Clavolonine (170 mg) was refluxed in AR hydriodic acid containing red phosphorus (0·6 g) for 100 hr. After cooling and filtering, the solution was basified with ammonia and chloroform extracted. The oil obtained on evaporation, crystallized on contact with acetone and was recrystallized from this solvent for analysis. The crystalline product, although homogeneous as shown by paper chromatography, had no definite melting point but decomposed over a wide range above 170°. (Found: C, 39·8; H, 5·1; N, 3·0; I, 52·4. $C_{16}H_{33}NI_2$ requires: C, 39·6; H, 5·2; N, 2·9; I, 52·3%).

Formation of cathylates

The procedure used for the reaction of deacetylfawcettiine with ethyl chloroformate was followed. The products were examined by paper chromatography and in the infra-red (chloroform solutions).

Hofmann degradation of clavolonine

To a solution of potassium (2·3 g) in dry tertiary butanol was added clavolonine methiodide (2·0 g) and the mixture refluxed for 60 hr and then evaporated to dryness under reduced pressure. The residue was taken up in water and extracted with chloroform, which was dried and then evaporated. The residue was recrystallized from acetone (550 mg). A portion was sublimed for analysis, m.p. 170–171°, $[\alpha]_D$ −30° (*c* 1·28 EtOH), I.R. 3500 (OH), 1685 (C:O) and 1425 (CH_2–CO) cm^{-1}. No absorption in the U.V. R.D. in EtOH (*c* 0·036) 25°; $[\alpha]_{589}$ −84°, $[\alpha]_{325}$ −1340°, $[\alpha]_{315}$ −980°. (Found: C, 73·6; H, 9·7; N, 5·0; O, 11·8; N–Me, 4·8. $C_{17}H_{27}NO_2$ requires: C, 73·6; H, 9·8; N, 5·0; O, 11·5; N–Me, 5·4%).

Acknowledgements—The authors wish to thank Dr. Z. Valenta (Univ. of New Brunswick) for performing the rotatory dispersions and NMR spectra, Dr. W. A. Ayer (Univ. of Alberta) for his co-operation concerning lycopodane and for a sample of lofoline and Mr. B. S. Mootoo for providing some of the samples for the optical rotation studies. We also thank Dr. F. A. L. Anet (Univ. of Ottawa) for comparing our sample of annofoline methiodide with an authentic specimen.

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STUDIES ON THE STEROIDAL COMPONENTS OF DOMESTIC PLANTS—XXXIV[1]

THE STRUCTURE OF LUVIGENIN, A NEW SAPOGENIN FROM *METANARTHECIUM LUTEO-VIRIDE* MAXIM.

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(*Received* 17 *January* 1961)

Abstract—A new steroidal sapogenin with an aromatic ring in the molecule was isolated from *Metanarthecium luteo-viride* Maxim., and proved to be 25D-19-nor-4-methyl-$\Delta^{1,3,5(10)}$-spirostatriene.

IN addition to two 11-hydroxy sapogenins, metagenin (Ia)[2] and nogiragenin (Ib)[3], *Metanarthecium luteo-viride* Maxim. contains luvigenin (II), m.p. 183–184°, $[\alpha]_D^{20}$ −34·9°, a new sapogenin having an aromatic ring in the molecule. The analytical values of luvigenin are in good agreement with the formula $C_{27}H_{38}O_2$ and its infra-red

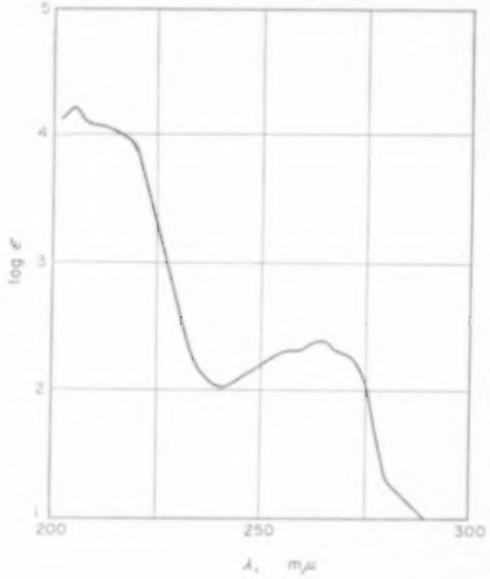
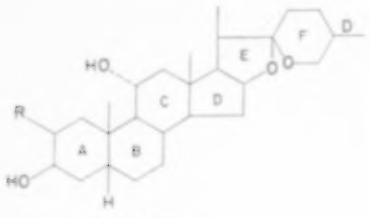


FIG. 1.

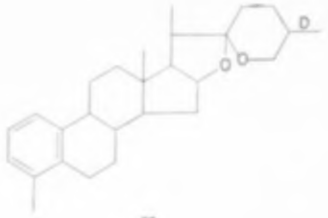
spectrum indicates not only the presence of ring E and F, but also that this sapogenin belongs to the 25D series by comparison of the intensities of the absorption bands at 923 and 900 cm^{-1}. It is interesting to note that luvigenin has only two atoms of oxygen, those present in rings E and F. This sapogenin is resistant to catalytic hydrogenation

[1] Part XXXIII: K. Sasaki, *Chem. Pharm. Bull.* In press.
[2] K. Takeda and K. Hamamoto, *Tetrahedron Letters* No. 3, 1 (1960).
[3] K. Takeda, T. Okanishi, H. Osaka, A. Shimaoka and N. Maezono, *Chem. Pharm. Bull.* In press.

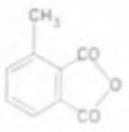
under usual conditions. The absorption maxima at 265 (ε 260) and 271 mμ (ε 200) in the ultra-violet spectrum (cf. Fig. 1) and at 785 and 740 cm^{-1} in the infra-red spectrum suggest the presence of a di- or tri-substituted benzene ring. Oxidation with 25 per cent nitric acid, although in small amount, yields toluene-2,3-dicarboxylic acid anhydride (III),[4] m.p. 113–115°, identical by mixed melting point and comparison of the infra-red spectra with an authentic specimen. Oxidation with 60 per cent nitric acid yields a mixture of benzene-1,2,3,4-tetracarboxylic acid (IVa) as its tetramethylester



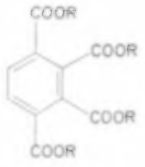
Ia R = OH
Ib R = H



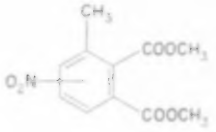
II



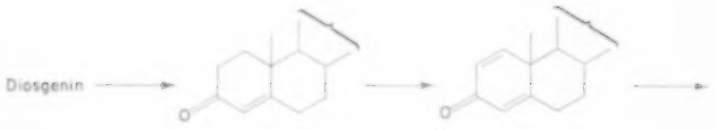
III



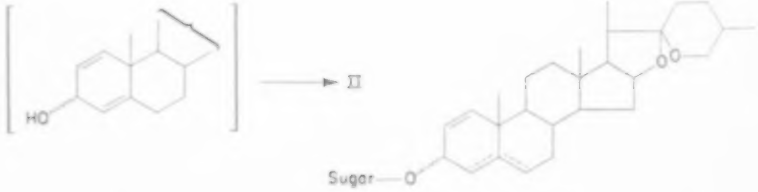
IVa R = H
IVb R = CH_3



V



VI VII



VIII IX

(VIb), m.p. 129–131°[5] (identical with the authentic specimen in all respects) together with a small amount of a nitro compound, m.p. 65–73°, which was assumed to be a mixture of x-nitrotoluene-2,3-dicarboxylic esters (V). Although these results indicate the presence of a naphthoid group in luvigenin this is not in agreement with the optical

[4] V. Jürgens, *Ber. Dtsch. Chem. Ges.* **40**, 4409 (1907).
[5] L. F. Fieser and M. A. Peters, *J. Amer. Chem. Soc.* **54**, 4347 (1932).

data. It would seem, therefore, that A ring of luvigenin is aromatic with one methyl group at C-1 or C-4 and that during oxidation aromatization of B ring takes place more readily than oxidative cleavage. Similar results have been observed by Wilds and Djerassi[6] in the oxidation of the $\Delta^{1,3,5(10)}$-cholestatriene derivative with concentrated nitric acid.

In 1958, the Scherling[7] and the Butenandt groups[8] reported independently the 1,4-dien-3-ol type rearrangement of some steroids, and in these papers they clarified that this type of rearrangement afforded the 4-methyl A-benzenoid steroid by the action of acid or magnesium silicate.

From these observations, the most probable structure for luvigenin appears to be 25D-19-nor-4-methyl-$\Delta^{1,3,5(10)}$-spirostatriene (II), and the synthesis of this compound from diosgenin has been achieved.

Diosgenin converted to diosgenone[9] was dehydrogenated to $\Delta^{1,4}$-titgogenone (VII), m.p. 200°, by the action of 2,3-dichloro-5,6-dicyanobenzoquinone.[10] This dienone was reduced with $LiAlH_4$ in tetrahydrofurane to the dienol (VIII) and treated with acetic acid without purification. The rearranged product, m.p. 183–184°, $[\alpha]_D$ −31·6°, was identical with luvigenin in all respects.

Since luvigenin has no hydroxyl group in the molecule, it may exist in the plant as a proto-type glycoside, where the aglycon takes a 1,4- or 1,5-dien-3-ol structure as represented by IX or its precursor and this proto-type sapogenin is converted to luvigenin during acid hydrolysis of the saponin mixture.

EXPERIMENTAL

All melting points are uncorrected. Unless otherwise stated, ultra-violet spectra were determined in 95% ethanol, optical rotations in chloroform, and infra-red spectra as "Nujol" mulls using a Koken Infra-red Spectrophotometer Model DS 301.

Extraction and purification of luvigenin (II)

The methanol extract of *Metanarthecium luteo-viride* Maxim. was treated with 6% ethanolic HCl on a water bath for 6 hr. After addition of water (5 l.) the ethanol was distilled off *in vacuo* and the water-insoluble product collected and saponified with methanolic KOH under reflux for 1 hr. The ether extract of the residue on treatment with cold acetone yielded crude metagenin (Ia) as a crystalline precipitate (ca. 0·4%). The filtrate was evaporated to dryness and the residue was dissolved in benzene and chromatographed.

The first eluted fraction gave luvigenin (II) as prisms, m.p. 178–180°, in 0·016% yield. Pure luvigenin, m.p. 183–184°, was obtained from methanol–chloroform recrystallization: $[\alpha]_D^{20}$ −34·9° (*c* 1·130), λ_{max} 205 (ε 16,000), 215 (ε 10,200), 265 (ε 260) and 271 mμ (ε 200); ν_{max} 3080, 1585 (benzene), 981, 923 < 900, 860 (ring F), 785, 740 cm^{-1} (benzene). (Found: C, 82·45; H, 9·67. $C_{27}H_{38}O_2$ requires: C, 82·18; H, 9·71%).

Nitric acid oxidation of luvigenin

(a) 25% *Nitric acid.* A mixture of luvigenin (1 g) and 25% HNO_3 (120 ml) was heated on an oil bath for 42 hr under reflux. After cooling, the reaction mixture was extracted with ether and the aqueous layer evaporated to dryness *in vacuo*. Both the ether layer and the residue from the aqueous solution was treated with 10% Na_2CO_3, and the combined solutions acidified with HCl, and extracted with ether. From the neutral ethereal fraction, 408 mg of luvigenin was recovered.

[6] A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.* **68**, 1712 (1946).
[7] M. J. Gentles, J. B. Moss, H. L. Herzog and E. B. Hershberg, *J. Amer. Chem. Soc.* **80**, 3702 (1958).
[8] H. Dannenberg and C. H. Doering, *Z. Physiol. Chem.* **311**, 84 (1958); **317**, 174 (1959).
[9] R. E. Marker, T. Tsukamoto and D. L. Turner, *J. Amer. Chem. Soc.* **62**, 2525 (1940).
[10] D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.* 14 (1960).

An oily acidic mixture (370 mg) was esterified with an ethereal solution of diazomethane and the ester distilled at 150–180° (bath temp)/0·4 mm. This oily ester (35 mg) was saponified and sublimed at 140–160° (bath temp)/0·1 mm. The sublimed substance was recrystallized from hexane to give needles, m.p. 113–115° (4 mg), (Found: C, 66·75; H, 3·98. $C_9H_6O_3$ requires: C, 66·67; H, 3·73%), which was identical with the authentic sample of toluene-2,3-dicarboxylic acid anhydride.

(b) 60% *Nitric acid.* A mixture of luvigenin (1·5 g) and 60% HNO_3 (45 ml) was refluxed for 24 hr. The reaction mixture was evaporated to dryness ether extracted and the residue treated with an excess of ethereal diazomethane. The resulting ester mixture was dissolved in benzene and chromatographed on alumina. The first eluted oily fraction (285 mg) was followed by a crystalline fraction. This second fraction on treatment with ether gave prisms (ca. 15 mg; IVb), m.p. 129–131°. The mother liquor was concentrated to dryness *in vacuo* and distilled under red press (b.p. 145–190° (bath temp)/0·005 mm) to give further 15 mg of the same ester, m.p. 130°. λ_{max} 208 (ε 29500) and 289 mμ (ε 1,340). (Found: C, 54·46: H, 4·66: OCH_3, 39·59. $C_{10}H_2O_4(OCH_3)_4$ requires: C, 54·19; H, 4·55: OCH_3, 40·00%). This was identical with synthetic tetramethyl mellophanate, m.p. 129–131°, by mixed m.p. and infra-red spectrum.

The first eluted oily fraction was dissolved in pet ether–benzene (1:1), rechromatographed, and was separated into two fractions: the pet ether–benzene fraction and the benzene fraction.

The first fraction distilled at 140–145° (bath temp/0·004 mm), and the distillate (90 mg) purified by charcoal and crystallized from a pet–ether and ether mixture afforded prisms, m.p. 65–73° (Monoscope). Further recrystallization of this substance from the same solvent did not show any change in m.p. Infra-red spectrum showed the following bands: ν_{max} 1738 (ester), 1608 (benzene) and 1538 and 1360 cm^{-1} (nitro group). From the presence of the absorption bands corresponding to the nitro group and the analytical values of this substance, it was assumed that this substance is a mixture of the position isomer of the nitro group in V. (Found: C, 51·84; H, 4·39: N, 5·96. $C_{11}H_{11}O_6N$ requires: C, 52·17: H, 4·38: N, 5·53%). Further a small amount of V and a crystalline substance, m.p. 73–76°, were obtained from the mother liquor. The latter was insufficient for further examination. Another crystalline substance (2 mg), m.p. 90–98°, was isolated from the second benzene eluate but this so far has not been examined.

Luvigenin from diosgenin

$\Delta^{1,4}$-*Tigogenone* (VII). Diosgenone (8 g) obtained from diosgenin by the Oppenauer oxidation,[9] was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (6 g) in absolute benzene under reflux for 33 hr until paper partition chromatography indicated the disappearance of diosgenone. After filtration, to the benzene solution (concentrated to half volume) ether (300 ml) and 2% KOH solution (300 ml) was added and the ether layer washed and dried. After removal of the solvent, the residue was purified by chromatography, followed by recrystallization from methanol; VII, m.p. 198–200°, yield 5·96 g (75%). $[\alpha]_D^{20}$ −78·7° (*c* 1·045): λ_{max} 245 mμ (ε 15,500). (Found: C, 79·13: H, 9·34. $C_{27}H_{38}O_3$ requires: C, 78·98: H, 9·33%).

1,4-*Dienol* (VIII) *and its rearrangement.* To a solution of VII (6 g) in a mixture of absolute ether (200 ml) and absolute tetrahydrofurane (40 ml) $LiAlH_4$ (3 g) in the same solvent was added at 0–5°. The mixture was heated under reflux for 1 hr, then ethanol and water were added and the organic layer yielded crude dienol (6 g, VIII). The mixture of this crude VIII (6 g), acetic acid (500 ml) and water (50 ml) was refluxed for 5 min and allowed to stand overnight. The crystalline precipitate was collected and recrystallized from methanol to give 1·7 g of the rearrangement product, m.p. 183–184°. Further addition of water (1·5 l.) to the mother liquor afforded another 363 mg of the same product. $[\alpha]_D^{27}$ −31·6° (*c* 1·065). (Found: C, 82·07: H, 9·87. $C_{27}H_{38}O_2$ requires: C, 82·18: H, 9·71%). This was identical with luvigenin by mixed m.p. and infra-red spectra. The above-mentioned mother liquor was evaporated to dryness and the residue was purified by chromatography. Elution with pet ether–benzene (10:1) afforded 163 mg of $\Delta^{5,5}$-25D-spirostadiene, m.p. 163–165°, $[\alpha]_D^{23}$ −178·8° *c* 1·025), λ_{max} 228 mμ (ε 22,800). (Found: C, 81·71: H, 10·26. $C_{27}H_{40}O_2$ requires: C, 81·76: H, 10·17%),[11] while with pet ether–benzene (1:1) yielded 290 mg of diosgenone.

[11] H. Nawa, *Proc. Japan Acad.* **33**, 570 (1957).

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THE AMINOLYSIS AND ESTERIFICATION OF UNSYMMETRICAL EPOXIDES

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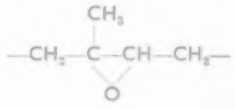
(*Received* 21 *March* 1961)

Abstract—The reactions of 1,2-epoxypropane (I) and 2-methyl-2,3-epoxypentane (II) with various primary and secondary amines and with hexahydrophthalic anhydride in the presence of hydroxylic catalysts have been studied. The direction of ring opening of the epoxides on reaction with the amines is unaltered by the presence of phenol as catalyst, and involves attack at the least substituted carbon atom of the epoxide ring. The structures of the piperidino adducts (*viz.* IV and V) derived from the phenol-catalysed reaction of piperidine with I and II, respectively, were proved by unambiguous syntheses of IV and V by the interaction of the corresponding chlorhydrin with piperidine. With hexahydrophthalic anhydride in the presence of water, I gave a low molecular weight polymeric ester whereas II afforded mainly a diadduct derived from the reaction of two molecules of II with one molecule of the anhydride. Reaction mechanisms are discussed briefly.

LITTLE work has been reported on the reaction of highly alkyl-substituted epoxides, particularly those derived from trialkylethylenes, with amines and carboxylic acid anhydrides in the absence of hydroxylic solvents. Results to be reported elsewhere[1] describe the partial or complete epoxidation of natural rubber to give modified rubbers which contain the epoxide structure III, and which can be subsequently crosslinked with bifunctional reagents such as primary diamines or carboxylic acid anhydrides. The present paper is concerned with the reactions of 1,2-epoxypropane (I) and 2-methyl-2,3-epoxypentane (II)—the latter being a model for natural rubber epoxide—with amines and a carboxylic acid anhydride.



III

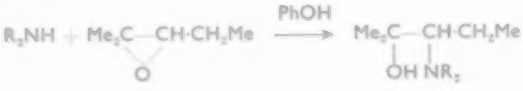
Aminolysis of epoxides. The data in Table 1 indicate the comparative reactivities of primary and secondary alkylamines with 2-methyl-2,3-epoxypentane (II) in the presence or absence of phenol as catalyst and in the absence of hydroxylic solvents. Interaction of II occurs with primary alkylamines but not with the more sterically-hindered diethylamine. n-Butylamine reacts only in the presence of phenol, this effect being in keeping with the known catalysis by phenols of the aminolysis of epoxides.[2] Primary alkyldiamines are more reactive than n-butylamine and yield both mono- and diadducts by reaction with either one or two molecules of the epoxide; the relative proportions of the mono- and di-adducts depend on the relative proportions of the reactants and catalyst (phenol). Reaction of piperidine with II under the conditions

[1] T. Colclough, to be published.
[2] L. Shechter, J. Wynstra and R. P. Kurkjy, *Industr. Engng. Chem.* **48**, 94 (1956).

TABLE 1. REACTION OF 2-METHYL-2:3-EPOXYPENTANE (II) WITH AMINES AT 140° (*in vacuo*)

Amine	Mole ratio Epoxide/amine/phenol	Reaction time (hr)	Yield of products (mole % initial amine) Monoadduct	Diadduct
Bu^nNH_2	1:1:0	40	0	—
Bu^nNH_2	1:1:0·1	40	70	—
$NH_2(CH_2)_2NH_2$	1:1:0	14	25	~5
$NH_2(CH_2)_2NH_2$	1:1:0·1	14	50	~45
$NH_2(CH_2)_2NH_2$	2:1:0·2	14	~20	80
$NH_2(CH_2)_6NH_2$	1:1:0·1	16	40	10
Et_2NH	1:1:0	5	0	—
Et_2NH	1:1:0·1	17	0	—
	1:1:1·0	40	100	—

specified in Table 1 gave a quantitative yield of 2-methyl-3-piperidinopentan-2-ol (V; Reaction 1), identified and estimated as its hydrochloride. Phenol was recovered in 94 per cent yield.

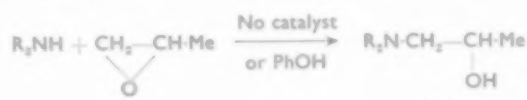


(1)

II V

(where R_2NH = piperidine)

The adduct V was synthesized unambiguously by interaction of 2-methyl-3-chloropentan-2-ol with piperidine under conditions leading to direct displacement of the chlorine atom by the piperidino group, i.e. without the intermediary formation of the epoxide.[3] Consistently, the interaction of 1,2-epoxypropane (I) with piperidine either in the absence or presence of phenol yields 1-piperidinopropan-2-ol (IV) as the sole product (Reaction 2), indicating that opening of the epoxide ring in these systems, as in others reported in the literature,[4] occurs by exclusive or predominant attack of the amine at the least substituted carbon atom. Reaction of I to give IV exclusively is also observed when water plus phenol is used to catalyse Reaction 2 and when piperidine is



(2)

I IV

(where R_2NH = piperidine)

replaced by piperidine hydrochloride. The aminoalcohol IV and the isomeric 2-piperidinopropan-1-ol (VI) were synthesized by reaction of piperidine with the appropriate α-chloroalcohol; under the reaction conditions used (see Experimental) both IV and VI were obtained free from their isomers, thus confirming that the aminoalcohols are

[3] L. R. Hawkins and R. A. B. Bannard, *Canad. J. Chem.* **36**, 220 (1958).

[4a] R. E. Parker and N. S. Isaacs, *Chem. Rev.* **59**, 737 (1959); [b] N. B. Chapman, N. S. Isaacs and R. E. Parker, *J. Chem. Soc.* 1925 (1959); 3497 (1960).

formed by direct displacement of the chlorine atom by the amine and not *via* the epoxide which then subsequently reacts with the amine.

The phenol catalysed reaction of 2-methyl-2,3-epoxypentane (II) with piperidine is much slower than the comparable reaction of the less alkyl-substituted 1,2-epoxypropane (Fig. 1). This feature, together with the orientation of addition of piperidine to II in the presence of phenol (Reaction 1) and the lack of reactivity of II towards

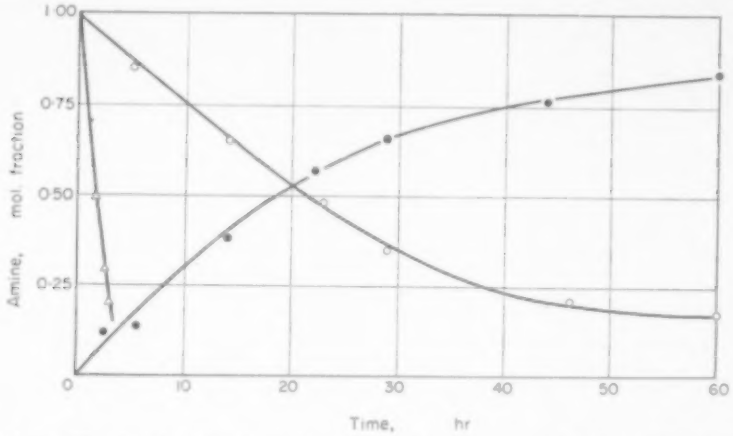
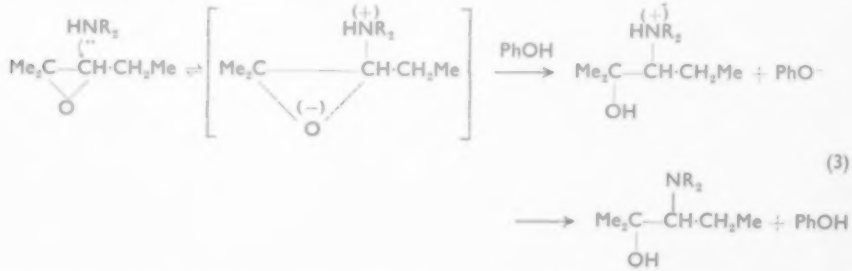


FIG. 1. The phenol-catalysed reactions of equimolar proportions of piperidine with: (a) 1,2-epoxy-propane at 60° (0·03 mole phenol per mole epoxide); and with (b) 2-methyl-2,3-epoxypentane at 140° (0·1 mole phenol per mole epoxide).
System (a) Δ, unreacted piperidine
System (b) ○, unreacted piperidine
●, 2-methyl-3-piperidinopentan-2-ol.

more sterically hindered secondary alkylamines (Table 1), suggests that Reaction 1 proceeds, as in the case of uncatalysed epoxide-amine interactions,[4a] by an S_N2 mechanism involving attack by the amine at the least substituted carbon atom of the epoxide ring. It is suggested that the function of the phenol or other hydroxylic material is to transfer a proton to the oxy-anion in the transition state:

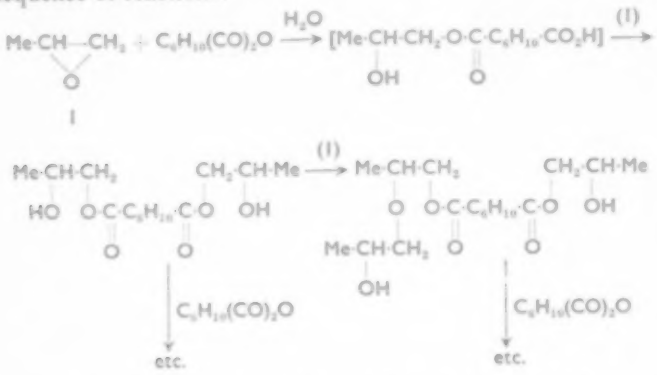


(3)

This mechanism implies that weakly acidic phenols should be more effective catalysts than alcohols or water, whereas stronger acids would be less effective than phenols since such acids would be effectively removed by salt formation with the amine. In keeping with this, no reaction occurs between piperidine *p*-toluene sulphonate and II under the conditions used for Reaction 1.

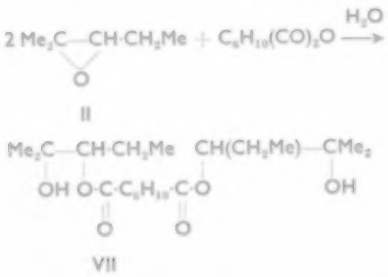
Reactions of epoxides with carboxylic acids and anhydrides. The complex nature of

the products resulting from epoxide-carboxylic acid interaction has been described by Hickinbottom and Hogg.[5] The several processes involved *viz*: esterification, etherification, dehydration and isomerization, and their relative proportions are dependent on the structure of the epoxide, the strength of the acid, and experimental conditions. For example, although trichloracetic acid is known to cause isomerization of 2,3-dimethyl-2,3-epoxybutane to a ketone[5] it does not isomerize II with which it reacts exothermically at 25°. Similarly, we have found quite different reactivities displayed by I and II when they are caused to react with hexahydrophthalic anhydride and water at 140°. Thus, the former epoxide gave a 90 per cent yield of a low molecular weight polymer containing both ester and ether groups,[6] suggesting the occurrence of the following sequence of reactions:



(4)

In contrast, the comparable reaction of the trialkylethylene epoxide (II) yielded small amounts of a saturated ketone, formed by isomerization of II, and a dimer of the epoxide together with the major product which analysed for the dihydroxyester (VII):



(5)

The direction of ring opening of the epoxides as given in Reactions 4 and 5 has not been unequivocally established, although it conforms with the results of Graham *et al.*[7] on the interaction of 1,2-epoxy-2,4,4-trimethylpentane with acetic acid. Indirect evidence for the attack of carboxylate groups at the least substituted carbon atom of unsymmetrical epoxide rings is that II, unlike I, did not form a polymer on reaction with the anhydride and water, this being attributed to the formation of *tertiary* hydroxyl groups as in VII which cannot react further with carboxylic acid or epoxide

[5] W. J. Hickinbottom and D. R. Hogg, *J. Chem. Soc.* 4200 (1954).
[6] R. F. Fischer, *J. Polymer Sci.* **44**, 155 (1960), and references therein.
[7] A. R. Graham, A. F. Millidge and D. P. Young, *J. Chem. Soc.* 2180 (1954).

functions. Consistent with this, the *tertiary* alcohol, 2-methylpentan-2-ol does not undergo esterification on reaction with hexahydrophthalic anhydride or succinic acid at 140°, but affords a mixture of Δ^1- and Δ^2-2-methylpentenes.

EXPERIMENTAL

Materials. 1,2-Epoxypropane, b.p. 37°/756 mm, was 100% pure when analysed by the method of Jungnickel *et al.*[9] using pyridine hydrochloride in chloroform as reagent. *2-Methyl-2,3-epoxypentane*, b.p. 97·2–97·8°/768 mm, n_D^{20} 1·3954 (Found: C, 71·8; H, 12·1; O, 16·4. $C_6H_{12}O$ requires: C, 71·9; H, 12·1; O, 16·0%) was obtained in 80% yield from the interaction of 2-methylpent-2-ene and perbenzoic acid in methylene dichloride at 0–5°, followed by fractionation of the crude epoxide through a 40-plate column, and was found by infra-red analysis to be free from phenyl, hydroxyl and carbonyl groups. 1-Chloropropan-2-ol, b.p. 76·4–77·4°/111 mm, n_D^{20} 1·4401 (Found: C, 37·7; H, 7·3; Cl, 38·3. Calc. for C_3H_7OCl: C, 38·1; H, 7·4; Cl, 37·6%) was prepared by the lithium aluminium hydride reduction of monochloroacetone[9] and 2-chloropropan-1-ol, b.p. 69·2–69·8°/70 mm, n_D^{20} 1·4394 (Found: C, 37·9; H, 7·7; Cl, 37·3%) was prepared by the comparable reduction of α-chloropropionyl chloride;[10] the infra-red spectra of the two chloroalcohols showed them to be free from carbonyl groups. *2-Methyl-3-chloropentan*-2-ol, b.p. 92–94°/84 mm, n_D^{20} 1·4445 (Found: C, 52·6; H, 9·6; Cl, 26·6. $C_6H_{13}OCl$ requires: C, 52·8; H, 9·6; Cl, 26·0%) was prepared from the reaction of 2-methylpent-2-ene with hypochlorous acid by the method of Wilson and Lucas[11]. Amines were dried and fractionated before use. Piperidine hydrochloride, m.p. 242°(Lit, 242°), was purified by recrystallization from ethanol and drying at 70°/0·1 mm; other amine hydrochlorides were recrystallized from methanol–ether mixtures. Hexahydrophthalic anhydride had b.p. 146°/15 mm, m.p. 36–37° (Found: C, 62·1; H, 6·5. Calc. for $C_8H_{10}O_3$: C, 62·4; H, 6·5%).

Preparation of reference compounds. 1-Piperidinopropan-2-ol, b.p. 105–110°/40 mm, was obtained in 86% yield from the interaction of piperidine (2 moles) and 1-chloropropan-2-ol (1 mole) for 16 hr at 140° *in vacuo*; it gave a hydrochloride, m.p. 159° (Found: N, 7·7; Cl, 19·6. Calc. for $C_8H_{18}NOCl$: N, 7·8; Cl, 19·7%). The comparable reaction of piperidine with 2-chloropropan-1-ol gave 2-piperidinopropan-1-ol (40%), b.p. 118°/80 mm, n_D^{20} 1·4680 (Found: C, 66·8; H, 12·0; N, 9·5. Calc. for $C_8H_{17}NO$: C, 67·1; H, 12·0; N, 9·8%), which gave a hydrochloride having m.p. 117–119° (mixed m.p. with 1-piperidinopropan-2-ol hydrochloride, 116–124°) (Found: C, 53·1; H, 10·1; N, 8·0. Calc. for $C_8H_{18}NOCl$: C, 53·5; H, 10·1; N, 7·8%). There were slight differences between the infra-red spectra of the two isomeric hydrochlorides, but it was not possible to distinguish between the two types of hydroxyl groups present.

2-Methyl-3-piperidinopentan-2-ol (94%) was obtained from the reaction of 2-methyl-3-chloropentan-2-ol (1 mole) with piperidine (2 moles) for 112 hr at 140° *in vacuo*; it was isolated as the *hydrochloride*, m.p. 152°. (Found: C, 59·2; H, 10·8; N, 6·7; Cl, 16·3. $C_{11}H_{24}NOCl$ requires: C, 59·6; H, 10·9; N, 6·3; Cl, 16·0%).

Reaction of epoxides with amines

General procedure. All reactions were conducted in sealed tubes *in vacuo*. Reaction products were analysed for secondary amino groups by use of the dithiocarbamate method[12] and for tertiary amino groups by the potentiometric titration method.[13] The Table 1 records the products resulting from the reaction of 2-methyl-2,3-epoxypentane with various primary and secondary amines at 140° in the presence or absence of phenol as catalyst.

Reaction of 1,2-epoxypropane with piperidine

Interaction of equimolar quantities of the two reactants for 16 hr at 140° gave 1-piperidinopropan-2-ol (100%), identified as its hydrochloride, which had m.p. and mixed m.p. with authentic compound,

[9] J. L. Jungnickel, E. D. Peters, A. Polgár and F. T. Weiss, *Organic Analysis* (Edited by J. Mitchell) Vol. 1, p. 127. Interscience, New York (1953).
[9] J. D. Edwards, W. Gerrard and M. F. Lappert, *J. Chem. Soc.* 348 (1957).
[10] W. Fickett, H. K. Garner and H. J. Lucas, *J. Amer. Chem. Soc.* **73**, 5063 (1951).
[11] C. E. Wilson and H. J. Lucas, *J. Amer. Chem. Soc.* **58**, 2396 (1936).
[12] F. E. Critchfield and J. B. Johnson, *Analyt. Chem.* **28**, 430 (1956).
[13] C. D. Wagner, R. M. Brown and E. D. Peters, *J. Amer. Chem. Soc.* **69**, 2609 (1947).

159° (Found: C, 53·7; H, 10·1; Cl, 19·6. Calc. for $C_8H_{18}NOCl$: C, 53·5; H, 10·1; Cl, 19·7%) and identical infra-red spectrum with that of the authentic compound. The infra-red spectrum differed slightly from that of 2-piperidinopropan-1-ol hydrochloride. Comparable reaction of the epoxide (1 mole) with (i), piperidine hydrochloride (1 mole), (ii) piperidine (1 mole) and phenol (0·1 mole), and (iii) piperidine (1 mole), phenol (0·1 mole) and water (1 mole) all gave the same 1-piperidinopropan-2-ol, (hydrochloride, m.p. and mixed m.p. 159°).

Reaction of 2-*methyl* 2,3-*epoxypentane with piperidine*

The reactants (1 mole each) and phenol (1 mole) were heated for 40 hr at 140° and the product was treated with aqueous alkali and then extracted with ether. Treatment of the dried etherial extract with hydrogen chloride gave 2-methyl-3-piperidinopentan-2-ol hydrochloride (100%), m.p. 153° and mixed m.p. with authentic compound 152°, (Found: C, 59·4; H, 10·7; N, 6·3; Cl, 16·3%), having an infra-red spectrum identical with that of the authentic compound. Phenol recovered from the reaction product was identified and estimated as its tribromide, m.p. 91° (94%).

Reaction of epoxides with hexahydrophthalic anhydride and water

(1) 1,2-*Epoxypropane*. Interaction of the epoxide (8·32 g, 2 mole), the anhydride (11·01 g, 1 mole and water (0·43 g, 0·33 mole) for 2·5 hr at 140° *in vacuo* gave a viscous product from which unreacted epoxide (11%), but no anhydride, was recovered on distillation at 140°/0·01 mm. Treatment of the residue with aqueous sodium hydroxide followed by ether extraction gave an ether-soluble fraction (12·2 g, 62 wt % of reactants) which was mainly a low polymer in the form of an ester of a 2:1 epoxide: dicarboxylic acid mixture, (Found: C, 60·1; H, 8·3; O, 30·6; M(ebul, benzene), 1160; Sapn. value, 142. Calc. for $(C_{14}H_{22}O_5)_4$, H_2O: C, 61·2; H, 8·2; O, 30·6%; M, 1099; Sapn. value, 137). Strong absorption in the infra-red spectrum of the polymer at 1730 cm^{-1} and at 1170 cm^{-1} could be attributed to ester and ether groups, respectively; absorption at 3530 cm^{-1} indicated the presence of —OH groups, but anhydride and 1,2-dicarboxylic acid groups appeared to be absent. Acidification of the aqueous alkali extract yielded a lower molecular weight condensation product of the reactants (5·7 g, 29 wt% of reactants), (Found: C, 58·7; H, 8·0; O, 31·2%; M(ebul, benzene), 390; Sapn. value 216; —CO_2H, 15·8 wt.%).

(2) 2-*Methyl*-2,3-*epoxypentane*. Heating a mixture of the epoxide (7·22 g, 2 mole), the anhydride (5·54 g, 1 mole) and water (0·27 g, 0·4 mole) *in vacuo* for 4 hr at 140° gave a product which on distillation afforded the following fractions: (i) a saturated ketone (1·8 g, 25% of epoxide), b.p. < 80°/760 mm, which is probably 2-methylpentan-3-one formed by isomerization of the epoxide; (ii) an unidentified product (1·6 g, 22% of epoxide), b.p. 26–37°/0·07 mm, (Found: C, 70·8; H, 11·9; O, 17·2; M(ebul, benzene), 202,190. Calc. for $C_{12}H_{24}O_2$: C, 71·9; H, 12·1; O, 16·0%; M, 200) which contained ether and hydroxyl groups but no carbonyl groups, and (iii) a viscous residue (8·3 g), undistillable at 140°/0·01 mm, which was probably mainly di-(2-methyl-2-hydroxy-3-pentyl) hexahydrophthalate contaminated with some unreacted anhydride (0·8 g) (Found: C, 64·9; H, 9·0; O, 26·0; Sapn. value 220; M(ebul, benzene), 362,357. Calc. for $C_{20}H_{36}O_6$: C, 64·6; H, 9·7; O, 25·8%; Sapn. value, 186; M, 372). The infra-red spectrum of (iii) was consistent with it being an hydroxy-ester or half-ester.

Reaction of 2-*methylpentan-2-ol with hexahydrophthalic anhydride and with succinic acid*

(1) After 4 hr heating at 140° a mixture of the alcohol (5·4 g, 2 moles) and anhydride (4·02 g, 1 mole) gave a volatile fraction (4·7 g), b.p. 65–67°/760 mm, identified by infra-red spectrometry as a mixture of 2-methylpent-1-ene (0·7 g) and 2-methylpent-2-ene (3·8 g). The residual crystalline solid was hexahydrophthalic acid (4·1 g), m.p. 182–184° (Found: C, 56·0; H, 7·4. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·1%).

(2) Reaction of the alcohol (7·4 g, 2 moles) with succinic acid (4·28 g, 1 mole) for 4 hrs at 140° yielded a volatile material (7·15 g), b.p. 54–76°/760 mm, comprising water and an olefinic mixture (Found: C, 86·0; H 14·0. Calc. for C_6H_{12}: C, 85·6; H, 14·4%) of 2-methylpent-1-ene (0·7 g) and 2-methylpent-2-ene (4·8 g). Succinic acid (96%), m.p. 185°, was recovered.

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ALTERED SELECTIVITY OF REDUCTION OF STEROIDAL CARBONYLS

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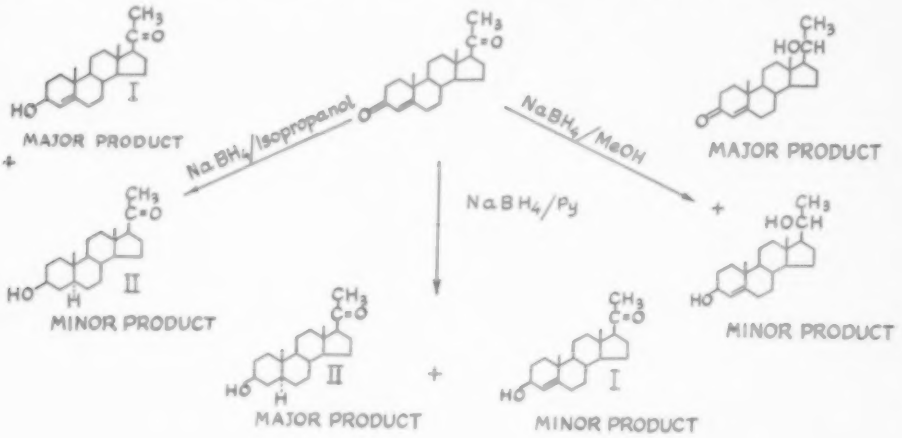
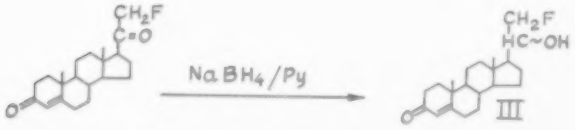
(*Received* 12 *April* 1961)

Abstract—The reduction of steroidal ketones in different solvents yielded different products. These conditions which altered the *normal* path, yielded a selective reduction of the Δ^4-3 carbonyl without the concomitant reduction of the C-17 or C-20 ketones; this permitted a one step partial synthesis of 3β-hydroxy-Δ^4-pregnen-20-one (I), 3β-hydroxy-5α-pregnan-20-one (II), and of 3β,11β-dihydroxy-androstan-17-one (IV).

CONSIDERABLE interest has been centered on 3β-hydroxy-Δ^4-pregnen-20-one (I) and related compounds as potential progestational substances. I has been previously prepared by classical procedures which involved lengthy multistep synthesis often with poor yields.[3,4] It was hoped that with the establishment of proper conditions such



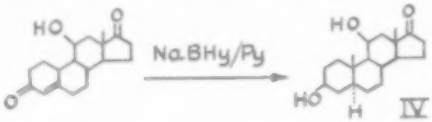


compounds might be prepared by a specific one step reduction of the C-3 group of the appropriate derivative using one of the metal hydrides. Such an approach was not previously attempted because preparative studies have demonstrated that the reactivity of steroid ketones with $NaBH_4$ does not follow a steric course; 20 ketone being reduced

[1] Present address: Biochemistry Section, Weizmann Institute of Science, Rehovoth, Israel.
[2] This investigation was aided by a grant from the Julius Schmid Company.
[3] M. Gut, *J. Org. Chem.* **21**, 1327 (1956).
[4] F. Sondheimer and Y. Klibansky, *Tetrahedron* **5**, 15 (1959).

preferentially to Δ^4-3 as demonstrated by the following order: 3 > 17 or 20 > Δ^4-3 > 11 ketone.[5–7] Selectivity of reduction was increased in the presence of pyridine.[6–10] While preparative studies which were conducted in MeOH with steroids containing multiple ketonic functions showed that 17 and 20 ketones were reduced preferentially to the Δ^4-3 ketone,[5] kinetic data with monoketonic steroids in anhydrous isopropanol indicated a reversed order,[11,12] i.e. Δ^4-3 > 17 > 20.

The present study demonstrates a method for the selective reduction of the Δ^4-3 carbonyl with $NaBH_4$ in anhydrous isopropanol to the 3β-hydroxy-Δ^4 compound without concomitant reduction of the C-20 carbonyl. Similarly with $NaBH_4$ in pyridine, reduction of the Δ^4 carbonyl was preferential to that of 17 and 20 ketones; but under these latter conditions saturation of the double bond also took place. On the other hand reduction of 21 fluoroprogesterone in pyridine followed the "normal" route and resulted with the exclusive reduction of the 20-carbonyl. These



IV

findings allowed the preparation of I and of 3β-hydroxy-5α-pregnan-20-one (II) from progesterone and the preparation of 3β,11β-dihydroxy androstan-17-one (IV) from 11β-hydroxy-Δ^4-androstene-3,17 dione by a one step reduction.

EXPERIMENTAL

3β-hydroxy-Δ^4-pregnen-20-one (I). Progesterone (200 mg) was dissolved in anhydrous isopropanol (32 ml) and sodium borohydride (25 mg) added. The resulting solution was mixed at room temp for 15 hr. Water (100 ml) was added and the resulting suspension extracted several times with ether. The ether phase was dried (Na_2SO_4) and evaporated to dryness under reduced press. Infra-red spectra of the resulting oil (ca. 200 mg) indicated an appearance of a band at 2·8 μ (OH) and a considerably larger decrease of the band at 6·0 and 6·15 μ (conj C=O) than at 5·9 μ (saturated C=O). The β-hydroxy derivatives were separated from the rest of the mixture by the conventional digitonide separation. The decomposition of the insoluble digitonide complex was achieved by dissolving in pyridine at room temp letting stand for 5 min followed by the addition of ether. The ether phase was washed with cold 0·2N HCl,[13] cold 5% aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness under vacuum. Colorless oil (ca. 100 mg) resulted. λ_{max}^{FILM} 2·90 (OH), 5·9 (C=O) and only minor band at 6·0 (Conj C=O) μ. Chromatography on 3 g of neutral alumina and elution with benzene–petroleum ether mixtures resulted in the isolation of 50 mg (25% yield) of crystalline substance; m.p. 156–159·5°; reported[2] m.p. 155–161°. λ_{max}^{KBR} 2·80 (OH), 5·92 (C=O) and 6·1 (c=c) μ; the infra-red spectrum was identical to an authentic sample prepared by a different route.[2]

3β-hydroxy-5α-pregnan-20-one (II). Progesterone (200 mg, 0·64 mmole) was dissolved in anhydrous pyridine (2 ml) containing $NaBH_4$ (50 mg, 1·2 mmoles). The resulting solution was mixed at room temp for 4½ hr. Water (100 ml) was added and the resulting suspension immediately extracted with

[5] J. K. Norymbarski and G. F. Woods, *J. Chem. Soc.* 3426 (1955).
[6] E. Eisberg, H. Vanderhaeghe and T. F. Gallagher, *J. Amer. Chem. Soc.* **74**, 2814 (1952).
[7] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1286 (1953).
[8] O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **74**, 3711 (1952).
[9] A. H. Soloway, A. S. Deutsch and T. F. Gallagher, *J. Amer. Chem. Soc.* **75**, 2356 (1953).
[10] N. N. Suvorov and Z. A. Varoslartsera, *Zh. Obsch. Khim.* **29**, 2889 (1959); *Chem. Abstr.* **54**, 12197 (1960).
[11] O. H. Wheeler and J. L. Mateos, *Canad. J. Chem.* **36**, 1049 (1958).
[12] J. L. Mateos, *J. Org. Chem.* **24**, 2034 (1959).
[13] Care should be taken to avoid prolonged contact with acid to avoid elimination of the allylic alcohol.

ether. The ether phase was washed with cold 0·2N HCl, 5% cold $NaHCO_3$ and water (till neutral); dried over Na_2SO_4 and evaporated under reduced pressure to dryness. The resulting oil (214 mg) showed in the infra-red, an insignificant reduction of the 20 ketone but a considerable reduction of the Δ^4-3 ketone and an appearance of a band at 2·75 μ (OH) λ_{max}^{ETOH} indicated 20% of residual conjugated ketone. Chromatography on silica gel and elution with benzene ethylacetate mixtures yielded 122 mg of crystalline material. Crystallization from ether and from acetone resulted in colorless plates; m.p. 189–192°; reported[14] m.p. 194°. The substance showed no absorption in the ultra-violet between 220–290 mμ and no U.V. absorption after prolonged acid treatment, which was indicative of no traces of allylic alcohol. Infra-red spectrum was identical to that of an authentic sample of 3β-hydroxy-5α-pregnan-20-one.

*21-fluoro-Δ^4-pregnen-*20-ol-3-*one* (III). 21-Fluoroprogesterone (m.p. 140–145°; 50 mg) was dissolved in pyridine (0·5 ml) to which was added $NaBH_4$ (12 mg). The solution was mixed at room temp for 4 hr. The reaction mixture was worked up similarly to that described for II resulting in 44 mg of oil. The infra-red spectrum indicated a total reduction of 20-ketone and practically no reduction of Δ^4-3 ketone. Chromatography on silica gel and elution with benzene–ethylacetate mixtures yielded a colorless oil. A fraction of this oil was chromatographed on paper in the ligroin–propylene glycol, located on paper by its U.V. absorption. Elution with methanol and methylene chloride resulted in a crystalline solid; m.p. 142–152°, λ_{max}^{KBr} 2·90 (OH), 6·0, 6·2 (conj C=O) and no band at 5·79 (α-fluoro C=O) λ_{max}^{MeOH} 241, ε = 13,100 (calculated for III). Oxidation of III without further purification by Py–Cro_3 complex yielded an oil λ_{max}^{Film} 5·80 (α-fluoro C=O) 6·05 (conj C=O) and no band at 2·90 μ (OH). The infra-red spectrum was identical to that of 21-fluoroprogesterone.

*3β, 11β-dihydroxy-androstan-*17-*one* (IV). 11β-Hydroxy-Δ^4-androstene-3, 17-dione (75 mg) was dissolved in cold pyridine (1 ml) containing $NaBH_4$ (19 mg) and mixed at room temp for 4½ hr. The reaction mixture was worked up similarly to that described for II (numerous extractions were required because of water solubility of the products).

Chromatography on neutral alumina, yielded colorless amorphous substance. Two crystallizations from ether yielded crystals melting at 228–231°; reported[15] 234–235°. The crystals showed no U.V. absorption in the ultra-violet between 220–290 mμ; λ_{max}^{KBr} 2·85 (OH), 5·80 (cyclopentyl C=O) and no absorption at 6–6·2 μ.

Results and Discussion

The method described permits a simple one step preparation of 3β-hydroxy-Δ^4-pregnen-20-one (I), 3β-hydroxy-5α-pregnan-20-one (II) and of 3β, 11β-dihydroxy-androstan-17-one (IV).

It is interesting to note that a mere change in the solvent employed had modified the site of $NaBH_4$ attack, i.e., the reduction of progesterone in MeOH resulted mainly in 20β-hydroxy-Δ^4-pregnen-3-one with an occasional formation of Δ^4-pregnen-3β, 20β-diol,[5] in isopropanol yielded mainly I with only small quantities of II and in pyridine yielded mainly II and occasionally significant quantities of I. But in no case could we demonstrate significant formation of 20β-hydroxy-Δ^4-pregnen-3-one in either isopropanol or pyridine.

Similarly the reduction of Δ^4-androstene-3,17-dione and Δ^4-androstene-3,11,17-trione in methanol yielded testosterone and 11-ketotestosterone respectively.[5] On the other hand, the reduction of 11β-hydroxy-Δ^4-androstene-3,17-dione in pyridine yielded IV; here again no 11β-hydroxy-testosterone could be demonstrated.

While the Δ^4-3 ketone is least hindered sterically and therefore should be most reactive, its slow reactivity has been attributed to resonance interactions which tend to reduce the charge on the ketone group.[11] Thus, conditions which will tend to decrease the importance of this interaction will tend to increase the reactivity of the Δ^4-3 ketone. This may well be the case when isopropanol and pyridine instead of methanol are employed.

[14] A. Butenandt and U. Westphal. *Ber. Dtsh. Chem. Ges.* **67**, 1440 (1934).
[15] J. von Euw and T. Reichstein. *Helv. Chim. Acta* **25**, 988 (1942).

Our results indicate that a delicate balance of steric and polar factors is at play and a slight shift in the magnitude of each will tend to effect the course of the reaction. This could be demonstrated in the reduction of 21-fluoroprogesterone in pyridine. The inductive effect of a vicinal fluorine has increased the reactivity of the C-20 carbonyl and allowed a selective reduction of the 20 carbonyl. Kinetic studies have demonstrated that the rate of reduction of 2-bromo-3-keto is ten fold that of the corresponding unsubstituted 3 keto.[12]

In addition, it is interesting to note that the reduction of Δ^4-3 keto groups with a large excess of $NaBH_4$ yielded saturated products, i.e. 3β-hydroxy-5α derivatives. While the reduction in isopropanol when the molar ratio of $NaBH_4$:steroid was 1:1, yielded primarily the allylic alcohol, a mere increase in this ratio to 2:1 yielded as much as 60 per cent of the saturated product. Similarly, progesterone-20-ethylene ketal in 90 per cent ethanol yielded the saturated derivative 5α-pregnan-3β-ol-20 ethylene ketal; the molar ratio of $NaBH_4$ to steroid was 10:1 and the reaction time was 16 hours.[4] On the other hand, a similar reaction in methanol with a lower molar ratio of $NaBH_4$ to steroid (3·5:1) and a shorter reaction time (2 hours) yielded 3β-hydroxy-Δ^4-pregnen-20-ethylene ketal in good yields.[3]

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PHOTOCHEMICAL TRANSFORMATIONS—VIII[1,2]

THE ISOMERIZATION OF $\Delta^{2,5}$-BICYCLO[2.2.1]HEPTADIENE TO QUADRICYCLO[2.2.1.$0^{2,6}$.$0^{3,5}$]HEPTANE (QUADRICYCLENE)[3]

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(*Received* 17 *March* 1961)

Abstract—$\Delta^{2,5}$-Bicyclo[2.2.1]heptadiene (III) upon ultraviolet irradiation was isomerized in 67 per cent yield to the valence tautomeric quadricyclene (IV) which, in turn, upon being heated, reformed III. The reactions of IV with hydrogen, with acetic acid and with bromine were studied.

IN 1954, Cristol and Snell[3] reported the first preparation of the quadricyclo-[2.2.1·$0^{2,6}0^{3,5}$] heptane ring system. Previous workers[5,6] had attempted the synthesis of parent compound of this ring system by purely chemical methods but met with no success. Cristol and Snell[3] found that $\Delta^{2,5}$-bicyclo[2.2.1]heptadiene-2,3-dicarboxylic acid (I) upon ultraviolet irradiation was readily transformed to its valence tautomeric structure (II) and they viewed the reaction as proceeding by activation of one of the carbon–carbon double bonds (most likely the unsaturated acid moiety) followed by reaction of this photoactivated bond with the other double bond. The conversion of carvone to carvone camphor is a similar photochemical reaction in which an activated double bond reacts with a near but not activated olefinic linkage.[7] However, on the basis of a

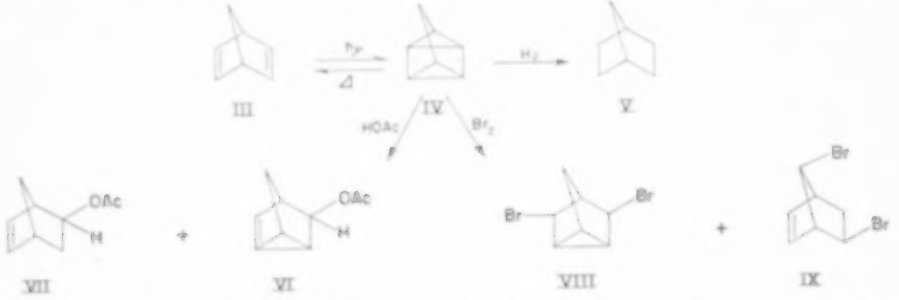
I II

study of the ultraviolet spectra of I and related materials, Jones, Mansfield and Whiting[8] have suggested that one of the excited electronic states in which the non-conjugated double bond interacts with the conjugated diacid system may be involved in this photochemical isomerization. Recently, Wilcox, Winstein and McMillan,[9] using semiempirical wave mechanical calculations, showed that in the lowest excited state (a complex band in the 215 mμ region) of the parent hydrocarbon, $\Delta^{2,5}$-bicyclo-[2.2.1]heptadiene (III), which contains no formally conjugated groups, there is interaction between the two isolated double bonds. If such an excited state is involved

[1] For paper VII, see W. G. Dauben, K. Koch, O. L. Chapman and S. L. Smith, *J. Amer. Chem. Soc.* **83**, 1768 (1961).
[2] This work was supported in part by Grant No. A–709 (C-6)-Bio, U.S. Public Health Service.
[3] For nomenclature, see S. J. Cristol and R. L. Snell. *J. Amer. Chem. Soc.* **80**, 1950 (1958).
[4] Postdoctoral Fellow, U.S. Public Health Service, 1960–1961.
[5] M. Lipp, *Ber. Dtsch. Chem. Ges.* **74**, 1 (1941).
[6] T. Hasselstrom and E. M. Falasco, Abstracts of Papers presented at the 125th Meeting of the American Chemical Society, Kansas City, Missouri, March, 1954, p. 39-N.
[7] G. Büchi and I. M. Goldman, *J. Amer. Chem. Soc.* **79**, 4741 (1957).
[8] E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.* 4078 (1956).
[9] C. F. Wilcox, S. Winstein and W. G. McMillan, *J. Amer. Chem. Soc.* **82**, 5450 (1960).

in the valence tautomeric reaction then it should be possible to convert III to the valence tautomeric IV, quadricyclene.[10]

When an ethereal solution of $\Delta^{2,5}$-bicyclo[2.2.1]heptadiene (III) was irradiated with a G.E. AH-6 high pressure mercury lamp, all the characteristic ultraviolet bands of III disappeared and the end absorption at 205 mμ dropped to about 25 per cent of the original value. Upon short path distillation, there was obtained in 67% yield a monomeric photoisomer (IV) which was saturated (ϵ_{210} 400). The irradiation product upon normal distillation slowly reverted to the starting diene and upon being heated in a sealed tube at 200–220° for 5 min the photoisomer was readily converted to III.



Such a heat induced reversal is characteristic of a valence tautomeric structure such as IV, quadricyclene. In line with the conclusion that no skeletal rearrangement had occurred was the finding that IV upon tetrahydrogenation yielded bicycloheptane (V).

The infrared spectrum of IV differed in the expected manner from that of the starting diene III. The latter compound possessed a band at 3040 cm^{-1} (olefinic hydrogen stretching)[11] the intensity of which was about one-third that of the 2990 cm^{-1} band of the saturated carbon-hydrogen absorption and also showed a very intense band at 725 cm^{-1}, characteristic of a *cisoid* disubstituted olefin[11]. The photoisomer possessed a band at 3050 cm^{-1}, characteristic of either olefinic or cyclopropyl hydrogens,[11] but the intensity of the band was equal to the 2990 cm^{-1} band. The *cisoid* disubstituted olefin band at 725 cm^{-1} was missing.

The nuclear magnetic resonance spectrum (Fig. 1) offered the best evidence for the quadricyclene structure. The spectrum showed only two bands[12] centered at 8·01τ and 8·59τ, clearly showing the absence of any vinyl protons. This feature, together with the ultraviolet end absorption, established the saturated character of the photoisomer. The 8·01τ band was a triplet (J = 1 cps) and represented the absorption of two protons. A triplet structure would be expected for the methylene hydrogens on C_7 when coupled with the hydrogen atoms on C_1 and C_4. The 8·59τ band was at least a quintuplet and represented the absorption for six protons. The structure of the band was typical of that found for an ab_2X_2 system in which the chemical shift between a and b is small.[13] Such would be the case for the hydrogens on the two

[10] The finding of Cookson and Crundwell [*Chem. & Ind.* 1004 (1958)] that Isodrin with two nonadjacent but interacting chromophores [λ_{max} 198 mμ (ϵ 9000)] was cyclized to Photodrin with ultraviolet light represents another example of this type of excited state.

[11] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*. John Wiley, New York (1956).

[12] We are indebted to Dr. Robert E. Lundin, Western Regional Research Laboratory, U.S. Department of Agriculture, for these measurements.

[13] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 126. McGraw-Hill, New York (1959).

cyclopropyl rings, the protons on C_1 and C_4 being slightly different from those on C_2, C_3, C_5 and C_6. Of particular interest was the position of these cyclopropyl hydrogen absorptions. In a simple substituted cyclopropane, such as norcarane (bicyclo[4.1.0]heptane), the methylene protons absorb at 9·98τ and the methine cyclopropyl protons at 9·29τ.[14] A similar methine cyclopropyl proton in nortryclene absorbs still lower at 8·99τ. Thus, the lowering of the cyclopropyl proton absorption

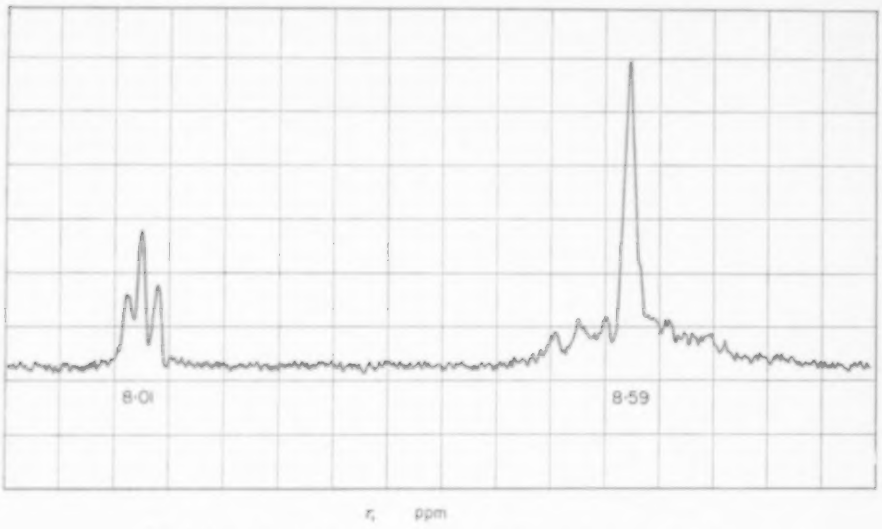


FIG. 1. NMR spectrum of quadricyclene (IV) in carbon tetrachloride.

to 8·59τ in quadricyclene is not surprising since the placement of the two connected cyclopropyl rings in adjacent planes could be expected to deshield the cyclopropyl hydrogens even more. A similar effect was found in the related diacid II of Cristol and Snell[3] in which the cyclopropyl protons absorb between 7·48–7·82τ. This extra lowering is due to a deshielding by the carboxylate group which in cyclopropanecarboxylic acid is known to lower absorptions by about 1τ unit (methylene protons in cyclopropanecarboxylic acid, 8·98–9·12).[14]

Quadricyclene was quite stable when stored, but, as would be expected for such a highly strained structure, the compound was quite reactive. When IV was allowed to stand for 26 hr at room temperature with glacial acetic acid, it was transformed into nortricyclyl acetate (VI) and *exo*-norbornenyl acetate (VII). Under the same conditions $\Delta^{2,5}$-bicyclo[2.2.1]heptadiene and nortricyclyl acetate were stable. Also, as was found by Cristol and LaLonde[15] with diacid II, bromine in carbon tetrachloride reacted rapidly with quadricyclene to yield a mixture of 2,6-dibromonortricyclene (VIII) and *exo*-5-anti-7-dibromonorbornene (IX).

This conversion of $\Delta^{2,5}$-bicyclo[2.2.1]heptadiene to quadricyclene by means of ultraviolet irradiation and the previous finding of Cookson and Crundwell[10] using Isodrin, point to the possibility of preparing highly strained systems by ring closure

[14] K. B. Wiberg, private communication.
[15] S. J. Cristol and R. T. LaLonde, *J. Amer. Chem. Soc.* **80**, 4355 (1958).

between any two isolated, but nearby, olefinic double bonds if the latter groups as measured by the ultraviolet absorption, show interaction in an electronic excited state.

EXPERIMENTAL[16,17]

Quadricyclo[2.2.1.$0^{2,6}$.$0^{3,5}$]*heptane* (*quadricyclene*) (IV)

A solution of 10 ml (9·0 g, 0·098 mole) of bicyclo[2.2.1]heptadiene[18] in 2 l. of dry ether was irradiated for 110 hr with a G.E. A-H 6 mercury lamp.[19] The ether was removed by distillation from a water-bath at 50° until the volume of the residue was about 50 ml. The concentrated solution was extracted with a saturated solution of silver nitrate, washed with water, dried, and concentrated by distillation to a volume of about 20 ml. The ethereal solution upon VPC, after the ether peak, showed one peak (DEGS,[20] ¼″ column, 48°, retention time, 8 min). The product was distilled through a short path still and arbitrarily three fractions of colorless distillate were collected, block temperature, 50–60°, 60–75°, and 75–77°. VPC analysis showed that each fraction contained a small amount of ether, approximately 95% of photo product and a few per cent of other substances (cycloheptatriene and toluene were absent), the yield was 6·0 g (67%) of a colorless liquid and there was 2 g of a yellow viscous residue. When the product was distilled in a normal Claisen flask, it slowly reverted to bicycloheptadiene but the b.p. was about 98°.

All physical measurements and subsequent reactions were carried out with pure samples of "quadricyclene" collected from VPC. The n_D^{20} was 1·4804 and the molecular weight as determined by mass spectrometry[21] was 92. In the ultraviolet there was no maximum only end absorption, ε_{206}^{EtOH}400. (Found: C, 91·41; H, 8·91. Calc. for C_7H_8(92·13): C, 91·25; H, 8·75%.)[22]

Pyrolysis of quadricyclene (IV) *to bicyclo*[2.2.1]*heptadiene* (III)

A sample of 109 mg (1·19 mmoles) of IV in a nitrogen atmosphere was sealed in a Pyrex tube and the tube was heated in a salt bath at 200–220° for 5 min. After cooling, the product was analyzed by VPC, using a DEGS column (10 ft by ¼″) at 35° and there were only two components, the ratio of the faster to the slower moving material was 2:1. The materials were separated using a ¼″ DEGS column at 50°. The material which appeared at 4 min was identified as bicyclo[2.2.1]heptadiene by infrared spectra and by VPC retention times. The minor, slower moving material (8 min) was unreacted quadricyclene.

Hydrogenation of quadricyclene (IV) *to bicyclo*[2.2.1]*heptane* (V)

A solution of 103 mg (1·12 mmoles) of IV in 15 ml of dry ether was hydrogenated over 26 mg of prereduced platinum oxide at atmospheric pressure and 23°. At the end of 25 min, 55 ml (2 mmoles) of hydrogen had been absorbed with no apparent change in rate during the hydrogenation. The catalyst was removed, most of the ether distilled (bath-temp. 50°) and the product collected from VPC (DEGS, ¼″, 35°). The infrared spectrum and the VPC retention time of the product were identical with those of an authentic sample of bicyclo[2.2.1]heptane, prepared by hydrogenation of bicyclo[2.2.1]heptadiene.

Reactions of quadricyclene (IV) *with acetic acid*

A solution of 62 mg (0·675 mmole) of IV in 1·0 ml of glacial acetic acid was allowed to stand under a nitrogen atmosphere for 26 hr. Ether (2 ml) and water (4 ml) were added and the excess acetic acid was neutralized with solid sodium bicarbonate. The two layers were separated and the water layer extracted again. From the combined ether layer two esters were isolated in approximately

[16] Analyses by the Microanalytical Laboratory, University of California, Berkeley.
[17] Identification by VPC means upon vapor phase chromatography that the unknown compound in question and the authentic material possessed identical retention times and when the two components were mixed, only a single peak was observed.
[18] Kindly supplied by the Shell Development Company, Emeryville, California.
[19] For details of the irradiation apparatus, see W. G. Dauben and R. L. Cargill, *Tetrahedron* **12**, 186 (1961).
[20] Diethylene glycol succinate, supplied by Wilkens Instrument Co.
[21] We are indebted to Dr. D. P. Stevenson, Shell Development Company, for this determination.
[22] The sample was dried over sodium.

equal amounts by the use of VPC (DEGS, 104°, 20 and 28 min). The faster moving fraction was shown to be nortricyclyl acetate by comparison in the usual manner with authentic material.[23] The slower moving fraction was identified as *exo*-norbornenyl acetate by the means of infrared spectra and VPC. An authentic sample of both the *endo* and the *exo* isomer was obtained from a mixture of the two acetates[24] by preparative VPC (¼" Glycerol column).

Reaction of quadricyclene (IV) *with bromine*

A solution of 213 mg (1·33 mmoles) of bromine in 1·2 ml of carbon tetrachloride was added, dropwise, to a solution of 111 mg (1·20 mmoles) of II in 1 ml of carbon tetrachloride at 0° in the dark. The bromine color was discharged immediately and heat was evolved. The resulting solution was colorless and the infrared spectrum of the reaction mixture was identical with that of an authentic mixture of 2,6-dibromonotricyclene and *exo*-5-*anti*-7-dibromonorbornene prepared by the addition of bromine to bicyclo[2.2.1]heptadiene.[25]

[23] We are indebted to Mr. G. H. Berezin for a sample of nortricyclenol.
[24] Kindly supplied by Professor J. D. Roberts and Dr. Marjorie C. Casserio.
[25] L. Schmerling, J. P. Lewis and R. W. Welch, *J. Amer. Chem. Soc.* **78**, 2819 (1956).
[26] S. Winstein, *J. Amer. Chem. Soc.* **83** 1516 (1961).

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ISOMERIC ESTRANE DERIVATIVES

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Abstract—Various 3,17-oxygenated isomeric estrane derivatives have been synthesized as possible metabolites of 19-norsteroids. Methods employed to establish configurations are described and biological data on some of the more pertinent compounds is presented.

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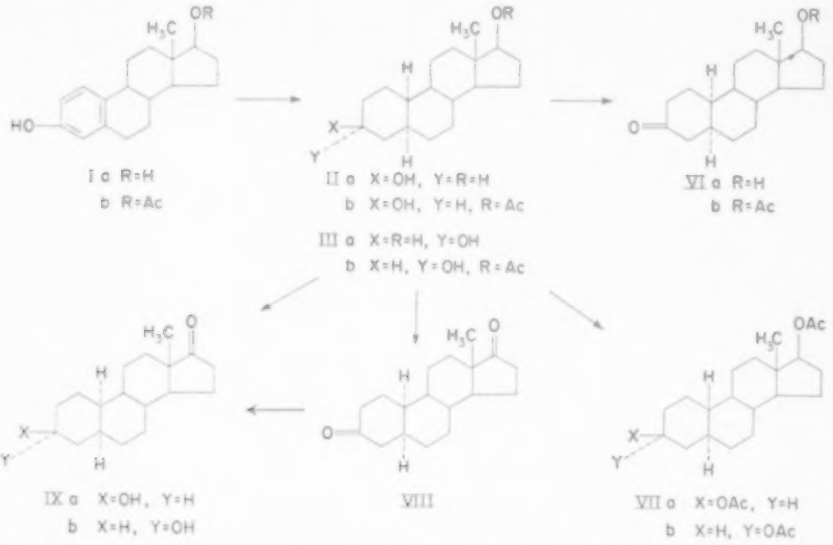
TESTOSTERONE and its esters have been used in therapy for their anabolic effects in many disease processes but treatment has been limited by the inherent androgenicity of the molecule. In 1953 Hershberger *et al.*[1] demonstrated that 19-nortestosterone (17β-hydroxyestr-4-en-3-one) retained the anabolic potency but was much less androgenic than testosterone propionate. In the past few years a number of modifications of 19-nortestosterone have been made in an effort to produce more potent anabolic agents possessing minimal androgenicity.[2–4] One approach to this problem involves the possibility that some metabolite of 19-nortestosterone may be the anabolicly active agent. As a consequence, the 19-nor analogs (estranes) of the *in vivo* metabolites of testosterone[5] were synthesized for biological evaluation. Since this work was initiated, a number of isomeric estrane derivatives have been synthesized[6–12] as well as isolated in metabolic studies.[13,14] This paper confirms the work of these investigators and attempts to clarify some of the structural discrepancies found in the literature as well as to describe the synthesis of other possible estrogen and norsteroid metabolites.

One path to the synthesis of the estranes is by catalytic hydrogenation of the aromatic "A" ring of the steroid estrogens. Hydrogenation with platinum catalyst has been employed for this purpose but causes extensive hydrogenolysis to monooxygenated products.[6,15] In their work on steroid total synthesis, Johnson and coworkers[16] reported that hydrogenations with ruthenium dioxide as catalyst reduced phenols with a minimum amount of hydrogenolysis. As a consequence, this catalyst was selected for the hydrogenation of the aromatic "A" ring.

[1] L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.* **83**, 175 (1953).
[2] F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *J. Amer. Chem. Soc.* **79**, 1123 (1957).
[3] J. Iriarte, C. Djerassi and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 436 (1959).
[4] B. Camerino, B. Patelli and A. Vercellone, *J. Amer. Chem. Soc.* **78**, 3540 (1956).
[5] *cf.* R. I. Dorfman and R. A. Shipley, *Androgens* p. 68. John Wiley, New York (1956).
[6] C. Chen, *Tetrahedron* **3**, 43 (1958).
[7] R. T. Rapala and E. Farkas, *J. Amer. Chem. Soc.* **80**, 1008 (1958).
[8] R. T. Rapala and E. Farkas, *J. Org. Chem.* **23**, 1404 (1958).
[9] A. Bowers, H. J. Ringold and R. I. Dorfman, *J. Amer. Chem. Soc.* **79**, 4556 (1957).
[10] A. Bowers, H. J. Ringold and E. Denot, *J. Amer. Chem. Soc.* **80**, 6115 (1958).
[11] D. Kupfer, E. Forchielli and R. I. Dorfman, *J. Org. Chem.* **25**, 1674 (1960).
[12] D. Kupfer, E. Forchielli and R. I. Dorfman, *J. Amer. Chem. Soc.* **82**, 1257 (1960).
[13] L. L. Engel, J. Alexander and M. Wheeler, *J. Biol. Chem.* **231**, 159 (1958).
[14] D. Kupfer, E. Forchielli and R. I. Dorfman, *J. Biol. Chem.* **235**, 1968 (1960).
[15] R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.* **62**, 73 (1940).
[16] W. S. Johnson, E. R. Rogier and J. Ackerman, *J. Amer. Chem. Soc.* **78**, 6322 (1956).

Of the four possible steric arrangements for the A/B rings in the estrane series, hydrogenation of estradiol (Ia) over ruthenium afforded the 5α,10α isomer (*cis-syn-trans*)[17] in excellent yield with no apparent hydrogenolysis. A similar finding was recently reported by Rapala and Farkas.[8] Thus, 5α,10α-estrane-3β,17β-diol (IIa) was obtained in 78 per cent yield. Chromatography of the mother liquors showed that the 3α epimer (IIIa) and 5β-estrane-3α,17β-diol (Va) were also formed in minor amounts. Although no 5β-estrane-3β,17β-diol (IVa) was isolated in this experiment, it was probably present in trace amounts (see below). IIa was also prepared by similar treatment of 17β-hydroxy-estr-5(10)-en-3-one. Considering that 19-nortestosterone is reduced by ruthenium catalysis to give products of the 5β,10β series,[7] it was conjectured that this catalyst may promote the hydrogenation of the difficultly reducible 5(10) double bond of estr-5(10)-ene-3,17-diol.[19] All attempts to reduce this compound, however, were unsuccessful.

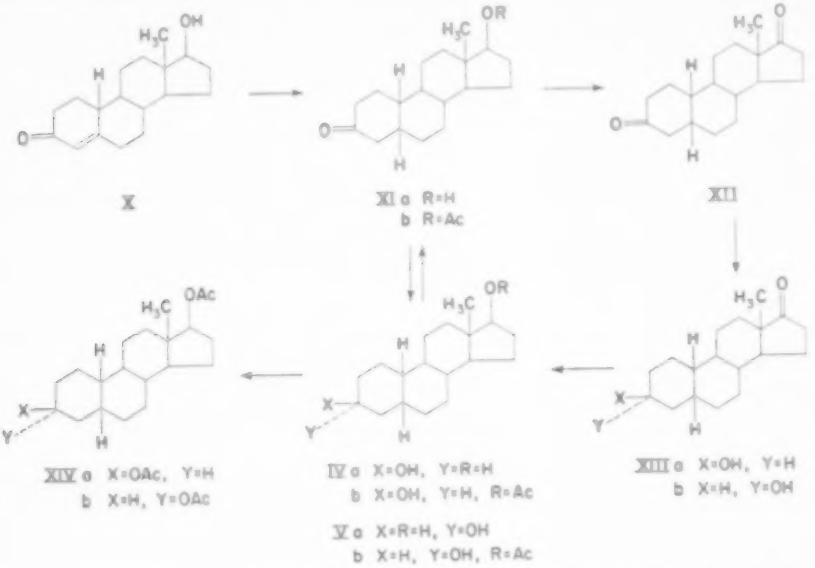


Four isomeric 17-monoacetates (IIb, IIIb, IVb and Vb) were obtained when estradiol 17-monoacetate was similarly hydrogenated. In this instance, 5β-estrane-3β,17β-diol 17-monoacetate (IVb), the isomer not obtained in the reduction of estradiol, was isolated and characterized. Hydrolysis of these monoacetates afforded the corresponding four isomeric diols, while oxidation by the Jones procedure[20] gave 5α,10α-estran-17β-ol-3-one acetate (VIb) and 5β-estran-17β-ol-3-one acetate (XIb) respectively. 5α,10α-Estrane-3,17-dione (VIII) was prepared by oxidation of the diol IIa.

Selective reduction of the C-3 carbonyl of VIII with non-pyrophoric W-2 Raney nickel catalyst according to the method of Djerassi[21] gave 5α,10α-estran-3β-ol-17-one

[17] The *trans-syn-trans* arrangement is energetically unfavored as it would require the "B" ring to assume a boat conformation.[18]
[18] W. S. Johnson, *Experientia* **7**, 315 (1951).
[19] J. A. Hartman, *J. Amer. Chem. Soc*, **77**, 5151 (1955).
[20] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39, (1946).
[21] C. Djerassi, A. J. Manson and M. Gorman, *J. Amer. Chem Soc.* **77**, 4925 (1955).

(IXa). Surprisingly, none of the 3α-epimer (IXb) could be isolated by this procedure. This isomer was prepared from 5α,10α-estrane-3α,17β-diol 17-monoacetate (IIIb) by initial formation of the 3-tetrahydropyranyl ether followed by basic hydrolysis of the 17-acetate group. The resulting product was oxidized and the 3α-hydroxyl group regenerated by acid hydrolysis of the pyranyl ether to give 5α,10α-estran-3α-ol-17-one (IXb). Acetylation of the 17-monoacetates IIb and IIIb gave the diacetates VIIa and VIIb, respectively.

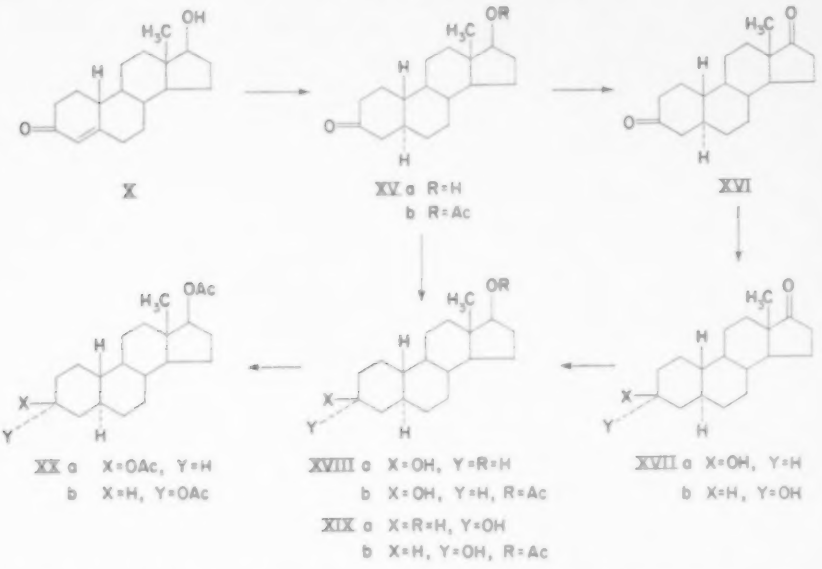


19-nortestosterone (X) was employed as the starting material for the preparation of the 5β and 5α-estranes. Low pressure hydrogenation over palladium-on-carbon gave 5β-estran-17β-ol-3-one (XIa) in good yield. A small amount 5β-estrane-3α,17β-diol (Va) was isolated by chromatography and found to be identical with Marker's estranediol B, of unknown configuration, isolated from human non-pregnancy urine.[22] Acetylation of this diol gave the diacetate XIVb in agreement with that of Marker's while oxidation of XIa gave 5β-estrane-3,17-dione (XII) identical with the reported estranedione B.[22] Reduction of this diketone with Raney nickel in ethanol gave the epimeric 5β-estran-3β-ol-17-one (XIIIa) and 5β-estran-3α-ol-17-one (XIIIb) (19-noretiocholanolone). Sodium borohydride reduction of these products furnished the diols IVa and Va which proved to be identical with those obtained by the hydrolysis of the corresponding 17-monoacetates.

5α-Estran-17β-ol-3-one (XVa) was prepared by reduction of 19-nortestosterone with lithium and liquid ammonia in a manner similar to that described by Bowers *et al.*[9,10] 5α-Estrane-3β,17β-diol (XVIIIa) was isolated as a minor by-product of this reduction. Oxidation of either of these two products or the crude reduction mixture gave 5α-estrane-3,17-dione (XVI). Selective reduction of this diketone with Raney nickel furnished 5α-estran-3β-ol-17-one (XVIIa) (19-norepiandrosterone) and 5α-estran-3α-ol-17-one (XVIIb) (19-norandrosterone). The latter was isolated by Engel

[22] R. E. Marker, E. Rohrmann, E. L. Wittle and E. J. Lawson, *J. Amer. Chem. Soc.* **60**, 1512 (1938).

and co-workers[13] from the urine of a patient after administration of 19-nortestosterone. An alternate synthesis of both these products was recently reported by Kupfer *et al.*[11,12] Reduction of 5α-estran-17β-ol-3-one (XVa) and its acetate (XVb) with Raney



nickel gave the epimeric diols XVIIIa and XIXa and their corresponding 17-monoacetates XVIIIb and XIXb. Acetylation furnished the diacetates XXa and XXb of which the former agrees with the product of unassigned configuration prepared by Hartman[19] by catalytic hydrogenation of estr-4-ene-3β,17β-diol diacetate.

The stereochemistry of the A/B ring fusion in the isomeric estranes has already

TABLE 1.—M_D INCREMENTS FOR CHANGES AT C-3

Type		Δ Ac (acetylation)	Δ Ket (ketonization)
5α	3α OH	+29 (+17)*	+57 (+66)
	3β OH	−30 (−29)	+67 (+73)
5β	3α OH	+113 (+82)	−16 (+7)
	3β OH	+15 (+17)	+20 (+36)

* The values for the 19 methyl steroids are in parentheses.[24]

been established.[7–9] The axial or equatorial configurations at C-3 were assigned on the basis of: (a) order of elution from the chromatographic column[23] (b) molecular rotation differences (c) position of C-0 frequencies between 1050 and 1000 cm^{-1} in the infrared and (d) nuclear magnetic resonance spectra.

Table 1 shows the molecular rotation differences (M_D) upon conversion of the

[23] The less polar axial isomer is followed by the more polar equatorial isomer upon elution.
[24] L. F. Fieser, *Steroids* p. 180. Reinhold, New York (1959).

epimeric C—3 alcohols into their acetates or corresponding ketones. It will be seen that the values obtained for isomeric 5α and 5β estranes are in good ageement with those obtained for the corresponding epimers in steroids possessing the C—19 angular methyl group.

The infrared spectra of the six isomeric estran-3-ol-17-ones gave further support to the configurational assignments at C—3. As noted by Cole and coworkers[25] equatorial

TABLE 2. HYDROXYL ABSORPTION BY AXIAL AND EQUATORIAL SUBSTITUENTS

Compound	Type	Conformation of C—O	ν(C—O) cm^{-1}
XVIIb	5α 3α OH	Axial	1010
XVIIa	5α 3β OH	Equatorial	1028
XIIIb	5β 3α OH	Equatorial	1032
XIIIa	5β 3β OH	Axial	995
IXb	5α, 10α 3α OH	Equatorial	1052
IXa	5α, 10α 3β OH	Axial	Complex

hydroxyl groups give rise to bands near 1040 cm^{-1} whereas for axial hydroxyl groups the C—O frequencies are near 1000 cm^{-1}. Table 2 shows the C—O frequencies for the isomeric estranolones. Whereas the values obtained for the 5α and 5β estranes support the assignments, the complex bands exhibited by 5α,10α-estran-3β-ol-17-one in this region made it impossible to draw conclusions for this series. The equatorial isomer, however, did exhibit an intense band at 1052 cm^{-1}.

Final proof of the configuration of the C—3 hydroxyls in the 5α,10α series was furnished by nuclear magnetic resonance studies.[26] Table 3 lists the τ values obtained for the C—3 proton of the six isomeric estranolones. These values are in agreement with those reported by Shoolery and Rogers for C—3 axial and equatorial protons in 3-hydroxy steroids.[27] The τ values for androsterone and epiandrosterone are shown for comparison.

The estrogen antagonistic action of some of these compounds has been published by our Biological Division.[28] Table 4 shows the androgenic and anabolic activities obtained for several of the more interesting compounds. The compounds exhibited a low order of activity compared to testosterone propionate, but it is interesting to note that the 3α-hydroxy compound (XIXb) in the A/B *trans* series is more active than the β-isomer (XIXa) as is the case in the normal series.[29] The compounds in the

[25] A. R. H. Cole, R. N. Jones and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 5571 (1952).
[26] I am indebted to Dr. McNiven, Worcester Foundation for Experimental Biology for the NMR data. The instrument employed for these measurements was a Varian High Resolution NMR Spectrophotometer Model V-4300B. The compounds were analyzed as 0·1 to 0·3 M. solutions in deuterochloroform using tetremethylsilane as the internal reference.
[27] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80**, 5121 (1958).
[28] R. A. Edgren, D. W. Calhoun, R. L. Elton and F. B. Colton, *Endocrinology* **65**, 265 (1959).
[29] R. I. Dorfman and R. A. Shipley, *Androgens* p. 118 John Wiley, New York (1956).

TABLE 3. NMR SHIFTS FOR PROTON ON 3-HYDROXY ESTRANES

Compound	Type	Proton Conformation	τ Value
XVIIb	3α OH	Equatorial	5·92
	5α		
XVIIa	3β OH	Axial	6·47
XIIIb	3α OH	Axial	6·41
	5β		
XIIIa	3β OH	Equatorial	5·89
IXb	3α OH	Axial	6·29
	5α, 10α		
IXa	3β OH	Equatorial	5·94
Androsterone	3α OH	Equatorial	5·87
	5α		
Epiandrosterone	3β OH	Axial	6·42

TABLE 4. ANDROGENIC-ANABOLIC ACTIVITY OF SOME ISOMERIC ESTRANE DERIVATIVES

Compound	Androgenic	Anabolic
Testosterone propionate	100	100
VIa	Inactive	Inactive
XIa	5	Inactive
XVa	10	20
XVIIIa	2	2
XIXa	5	5

5α,10α series were inactive in a variety of endocrinological assays including antiandrogenic, estrogenic, antiestrogenic, progestational, and antiprogestational.[30]

EXPERIMENTAL[31]

Hydrogenation of estradiol. To a solution of estradiol (20 g) in ethanol (500 ml) containing 40% sodium hydroxide solution (1 ml) was added ruthenium dioxide (5 g) and the mixture hydrogenated at elevated pressure (1475 lb/in²) and 65°. After hydrogen uptake ceased (2 hr), the catalyst was removed by filtration and washed well with ethanol. The filtrate was neutralized with acetic acid and the solvent removed by distillation under reduced pressure. Crystallization of the crude product from methanol–water afforded needles (11·9 g), m.p. 177–179°. Sublimation gave an analytical sample of

[30] Private communication from our Endocrinology Division.

[31] All melting points are uncorrected and all rotations were taken in chloroform. The infrared spectra were obtained with a Beckman model IR 4 spectrophotometer using 3% chloroform solutions. I am indebted to Dr. R. T. Dillon and Dr. H. W. Sause of our company for the analytical and microanalytical data.

5α,10α-estrane-3β,17β-diol (IIa), m.p. 180–182° (reported[a] 179–181°), $[\alpha]_D^{25}$ −12°. (Found: C, 77·3; H, 10·7. Calc. for $C_{18}H_{30}O_2$: C, 77·6; H, 10·9%). Adsorption of the residue on silica gel and elution with benzene–ethyl acetate (15%) gave an additional 4·0 g of the above diol. This was followed by minor amounts of the epimeric 5α,10α-estrane-3α,17β-diol (IIIa) m.p. 223–225°, $[\alpha]_D^{25}$ −6°. (Found: C, 77·5; H, 10·6. $C_{18}H_{30}O_2$ requires: C, 77·6; H, 10·9%) and 5β-estrane-3α,17β-diol (Va) (see below).

Hydrogenation of estradiol 17-monoacetate. To a solution of estradiol 17-monoacetate (20 g) in ethanol (1) was added ruthenium dioxide (7·0 g) and the mixture hydrogenated at 900 lb/in² and 55°. After hydrogen uptake ceased (2 hr), the catalyst was removed by filtration, washed well with ethanol, and the solvent removed from the filtrate. The residue was dissolved in a minimum amount of benzene and adsorbed onto silica gel (1700 g). Elution with benzene–ethyl acetate (5%) gave 5α,10α-estrane-3β,17β-diol 17-monoacetate (IIb, 12·1 g), m.p. 118–120° as the major product. Recrystallization from methanol–water gave an analytical sample, m.p. 125·5–127°, $[\alpha]_D^{25}$ −25°. (Found: C, 75·3; H, 10·0. $C_{20}H_{32}O_3$ requires: C, 75·0; H, 10·1%). Further elution gave 5β-estrane-3β,17β-diol-17-monoacetate (IVb, 0·95 g), m.p. 159–160·5°, $[\alpha]_D^{25}$ +15°. (Found: C, 74·6; H, 10·1). These were followed by the more polar 5α,10α-estrane-3α,17β-diol 17-monoacetate (IIIb, 2·25 g), m.p. 126·5–128·5°, $[\alpha]_D^{25}$ −24°. (Found: C, 75·2; H, 10·0), and 5β-estrane-3α,17β-diol-17-monoacetate (Vb, 2·4 g), m.p. 120–122°, $[\alpha]_D^{25}$ +26°. (Found: C, 75·0; H, 9·9).

5α,10α-*Estran*-17β-*ol*-3-*one acetate* (VIb). 5α,10α-Estrane-3β,17β-diol 17-monoacetate (IIb, 2·0 g) was dissolved in acetone (20 ml) and standard chromium trioxide reagent[20] added dropwise with stirring to the cooled solution until a faint color of the reagent persisted. Isopropanol was added to destroy the excess reagent and the supernatant solution poured slowly into ice-water. The resulting precipitate was removed by filtration and washed with water. Recrystallization of the crude product from ethanol–water afforded an analytical sample m.p. 112–112·5°, $[\alpha]_D^{25}$ −58·5° (reported[6] m.p. 110–111°, $[\alpha]_D^{25}$ −55·4 [acetone]). (Found: C, 75·3; H, 9·5. Calc. for $C_{20}H_{30}O_3$: C, 75·4; H, 9·5%).

5α,10α-*Estran*-17β-*ol*-3-*one* (VIa). The acetate VIb (2·0 g) was dissolved in methanol (49 ml) and water (1 ml). Potassium hydroxide flakes (1·0 g) was added and the solution refluxed for 1 hr. After allowing the solution to cool, water was added slowly with stirring. The resulting precipitate was removed by filtration and washed with water to give 1·8 g of product. Alternate recrystallizations from acetone–Skellysolve B and methanol–water produced an analytical sample, m.p. 149·5–150·5°, $[\alpha]_D^{25}$ −53°.[22] (Found: C, 78·2; H, 10·2. Calc. for $C_{18}H_{28}O_2$: C, 78·2; H, 10·2%).

5α,10α-*Estrane*-3β,17β-*diol diacetate* (VIIa). 5α,10α-Estrane-3β,17β-diol 17-monoacetate (IIb, 0·5 g) was dissolved in a mixture of pyridine (9 ml) and acetic anhydride (1 ml). The solution was heated on the steam bath for 4 hr and allowed to stand overnight at room temperature. The solution was poured slowly into ice-water and the resulting gum extracted with ether. The ether extract was washed with 2 N hydrochloric acid, 5% sodium carbonate solution, and water. After drying the solution over anhydrous potassium carbonate, the solvent was removed by distillation. Two recrystallizations of the crystalline residue from ethanol–water afforded needles, m.p. 103–104°, $[\alpha]_D^{26}$ −25. (Found: C, 73·1; H, 9·6. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α,10α-*Estrane*-3α,17β-*diol diacetate* (VIIb). Acetylation of 5α,10α-estrane-3α,17α-diol 17-monoacetate (IIIb) with acetic anhydride-pyridine gave, after several crystallizations from ethanol–water, the diacetate, m.p. 110·5–111°, $[\alpha]_D^{25}$ −30°. (Found: C, 72·6; H, 9·2. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α,10α-*Estrane*-3,17-*dione* (VIII). 5α,10α-Estrane-3β-17β-diol (IIa, 5·0 g) was dissolved in acetone (200 ml) and oxidized with standard chromium trioxide reagent as described above. This resulted in 3·9 g of product m.p. 157–160° and recrystallization from methanol–water gave an analtyical sample, m.p. 158–161°, $[\alpha]_D^{25}$ +24° (reported 8 m.p. 163–165°, $[\alpha]_D$ +27·5° [Dioxane]). (Found: C, 78·6; H, 9·4. Calc. for $C_{18}H_{26}O_2$: C, 78·8; H, 9·5%).

5α,10α-*Estran*-3β-*ol*-17-*one* (IXa). To a solution of 5α,10α-estran-3,17-dione (VIII, 2·4 g) in ethanol (200 ml) was added a slurry of aged W-2 Raney nickel catalyst (5 g) in ethanol. The mixture was refluxed with stirring for 4 hr and the catalyst removed by filtration. The solvent was removed from the filtrate and the residue dissolved in benzene (25 ml). Adsorption on silica gel (220 g) and elution with benzene–ethyl acetate (5%) afforded starting dione (0·44 g) followed by 5α,10α-estran-3β-ol-17-one (1·18 g). Alternate recrystallization from ethanol–water and Skellysolve C afforded an

[22] Rapala and Farkas[8] reported m.p. 192–194°, $[\alpha]_D$ −31·1° for this compound. Our constants are in more agreement with those of Chen[6] who reported m.p. 135°/146°, $[\alpha]_D^{23}$ −54·1° (acetone).

analytical sample, m.p. 152–154°, $[\alpha]_D^{28}$ +64°. (Found: C, 78·4; H, 10·0. $C_{18}H_{28}O_2$ requires: C, 78·2; H, 10·2%). Further elution with benzene–acetate (10%) gave a trace of 5α,10α-estrane-3β,17β-diol (IIa) identical with an authentic sample. This product was also prepared by reduction of IXa with sodium borohydride.

5α,10α-Estran-3α-ol-17-one (IXb). 5α,10αEstran-3α,17β-diol 17-monoacetate (IIIb, 2·0 g), dihydropyran (3 ml), and *p*-toluene sulfonic acid monohydrate (0·03 g) were dissolved in benzene (30 ml). After allowing the solution to stand overnight at room temperature, ether (100 ml) was added and the resulting solution washed successively with 5%-sodium bicarbonate solution and water. The organic phase was dried over anhydrous sodium sulfate and the solvent removed by distillation. The residue was dissolved in methanol (58 ml) and water (2 ml), sodium hydroxide flakes (1·0 g) added, and the solution refluxed for 1 hr. Glacial acetic acid (1·5 ml) was added and the solution concentrated to one third its original volume. Ether (100 ml) was added and the solution washed with water, 2 N hydrochloric acid, 10% sodium bicarbonate solution, and water respectively. After drying over anhydrous sodium sulfate, the solvent was removed and the oily residue dissolved in acetone (40 ml). Oxidation with chromium trioxide reagent in the usual manner afforded a gum when the solution was poured into ice-water. The product was extracted with methylene chloride and ether and the solvents removed by distillation. The residue was dissolved in methanol (30 ml), *p*-toluene sulfonic acid monohydrate (0·3 g) added, and the solution allowed to stand overnight at room temperature. The solution was poured slowly into ice-water and the resulting crystalline product removed by filtration. The crude product (1·6 g) was dissolved in benzene and the solution adsorbed on silica gel (85 g). Elution with benzene-ethyl acetate (10%) afforded 5α,10α-estran-3α-ol-17-one, m.p. 149·5–151°, $[\alpha]_D^{26}$ +64° after crystallization from acetone–Skellysolve C. (Found: C, 78·3; H, 10·1. $C_{18}H_{28}O_2$ requires: C, 78·2; H, 10·2%). Admixture with the 3β-epimer (Xa) caused a marked depression in the melting point (115–125°).

5β-Estran-17β-ol-3-one (XIa). To a solution of 19-nortestosterone (8·0 g) in ethanol (50 ml) containing potassium hydroxide (0·2 g) was added a slurry of 5% palladium-on-carbon (4 g) in ethanol (50 ml). Hydrogenation was carried out in a Parr low pressure hydrogenator at room temperature and the catalyst removed by filtration. The filtrate was neutralized with acetic acid and concentrated to one half its original volume. This solution was added dropwise with stirring to ice-water and the product removed by filtration. Adsorption of the residue from benzene onto silica gel and elution with benzene–ethyl acetate (20%) gave 5β-estran-17β-ol-3-one, m.p. 98–106°. Several recrystallizations from ether–Skellysolve B raised the m.p. to 108–110°, $[\alpha]_D^{25}$ +39° (reported[7] m.p. 106–108°; $[\alpha]_D$ +29·7° [Dioxane]). (Found: C, 78·0; H, 9·9. Calc. for $C_{18}H_{28}O_2$: C, 78·2; H, 10·2%). Further elution with benzene–ethyl acetate (40%) afforded a small amount of 5β-estrane-3α,17β-diol (Va) m.p. 204–206°, undepressed by admixture with an analytical sample (see below).

5β-Estran-17β-ol-3-one acetate (XIb). 5β-Estran-17β-ol-3-one (XIa) was acetylated by treatment with pyridine and acetic anhydride overnight at room temperature. The solution was poured slowly into ice-water and the crude product collected by filtration. Crystallization from methanol–water gave needles, m.p. 115–116/130–131·5°, $[\alpha]_D^{25}$ +29°.[33] (Found: C, 75·5; H, 9·6. Calc. for $C_{20}H_{30}O_3$: C, 75·4; H, 9·5%). This product was also obtained by oxidation of IVb and Vb with chromium trioxide reagent.

5β-Estrane-3,17-dione (XII). Oxidation of crude XIa (3·0 g) with chromium trioxide reagent in the usual manner and crystallization of the crude product from methanol–water gave 1·5 g of product, m.p. 181–183°. Alternate recrystallization from acetone–Skellysolve B and methanol–water gave an analytical sample, m.p. 182·5–185°, $[\alpha]_D^{25}$ +113° (reported[7] 179–181°, $[\alpha]_D$ +111·6°). (Found: C, 78·3; H, 9·4. Calc. for $C_{18}H_{26}O_2$: C, 78·8; H, 9·5%). An additional 0·8 g of product was obtained by chromatography of the residue from the mother liquor on silica gel.

Raney nickel reduction of 5β-estrane-3,17-dione. To 5β-estrane-3,17-dione (4·0 g) in ethanol (300 ml) was added aged W-2 Raney nickel catalyst (10 g) in the form of a slurry in ethanol. The mixture was refluxed with stirring for 2 hr and the catalyst removed by filtration. The solvent was removed from the filtrate and the residue taken up in benzene (40 ml) and placed on a column of silica gel (400 g). Elution with benzene–ethyl acetate (10%) gave a trace of starting material (0·5 g) followed by 5β-estran-3β-ol-17-one (XIIIa, 2·0 g) m.p. 157–164°. Several recrystallizations from ethanol–water gave an analytical sample m.p. 165–166·5°, $[\alpha]_D^{26}$ +108·5°. (Found: C, 78·1; H, 10·0.

[33] This product agrees with the compound obtained by Chen[6] (m.p. 114°/132·5°, $[\alpha]_D^{15}$ +28·2° [acetone]) to which the 5α configuration was assigned.

$C_{19}H_{32}O_2$ requires: C, 78·2; H, 10·2%). Further elution with benzene–ethyl acetate (15%) gave 5β-estran-3α-ol-17-one (XIIIb, 1·1 g), m.p. 167–167·5°, $[\alpha]_D^{25}$ +114·2° after recrystallization from ethanol–water. (Found: C, 78·2; H, 10·3. $C_{19}H_{32}O_2$ requires: C, 78·2; H, 10·2%). Admixture with the 3β epimer caused a marked depression in the melting point.

5β-Estrane-3β-17β-diol (IVa). To a solution of 5β-estran-3β,17β-diol-17-monoacetate (IVa, 0·2 g) in methanol (9·8 ml) and water (0·2 ml) was added potassium hydroxide flakes (0·1 g). The solution was refluxed for 1 hr and allowed to cool to room temperature. Water was added slowly with stirring and the resulting precipitate removed by filtration. Crystallization from acetone-Skellysolve C gave the diol (IVa) m.p. 127–131°, raised by recrystallization from methanol–ethyl acetate to 131–133°/154–157°, $[\alpha]_D^{25}$ +21·8°.[24] (Found: C, 77·7; H, 10·6. $C_{18}H_{30}O_2$ requires: C, 77·6; H, 10·9%). This product was also obtained by sodium borohydride reduction of XIIIa.

5β-Estrane-3α,17β-diol (Va). To a solution of 5β-estran-3α-ol-17-one (XIIIb, 0·05 g) in ethanol (10 ml) was added sodium borohydride (0·05 g) and the solution was allowed to stand overnight at room temperature. The solution was poured slowly into ice-water and the resulting precipitate removed by filtration and washed with 2 N hydrochloric acid and water. Recrystallization of the crude product from ethanol–water afforded an analytical sample, m.p. 207–208°, $[\alpha]_D^{25}$ +29·8° (reported[7] m.p. 211–212°, $[\alpha]_D$ +10·2°). (Found: C, 77·6; H, 10·9. Calc. for $C_{18}H_{30}O_2$: C, 77·6; H, 10·9%). This product was also obtained by hydrolysis of the monoacetate Vb and as a by-product in the catalytic hydrogenation of 19-nortestosterone.

5β-Estrane-3β,17β-diol diacetate (XIVa). A solution of 5β-estrane-3β,17β-diol (IVa, 0·25 g) in acetic anhydride (1 ml) and pyridine (9 ml) was heated on a steam bath for 2 hr. The cooled reaction mixture was poured slowly into ice-water and the resulting precipitate removed by filtration. Recrystallization from Skellysolve C gave an analytical sample, m.p. 113·5–115°, $[\alpha]_D^{25}$ +17°. (Found: C, 73·2; H, 9·5. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5β-Estrane-3α,17β-diol diacetate (XIVb). Acetylation of 5β-estrane-3α,17β-diol as described above afforded after several crystallizations from Skellysolve C needles, m.p. 160–162°, $[\alpha]_D^{25}$ +54°. (Found: C, 72·9; H, 9·3. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α-Estran-17β-ol-3-one (XVa). 19-nortestosterone was reduced with lithium in liquid ammonia essentially as described by Bowers *et al.*[10] except that tetrahydrofuran previously distilled from methyl magnesium iodide was used as solvent. The crude product was adsorbed from benzene onto silica gel and eluted with benzene containing increasing amounts of ethyl acetate. Elution with benzene–ethyl acetate (15%) and crystallization of the product from acetone–Skellysolve C gave 5α-estran-17-β-ol-3-one, m.p. 133–134°, $[\alpha]_D^{25}$ +59·5° (reported[10] m.p. 130–132°, $[\alpha]_D$ +60°). (Found: C, 77·9; H, 10·2. Calc. for $C_{18}H_{28}O_2$: C, 78·2; H, 10·2%). Further elution with benzene–acetate (25%) gave a trace of 5α-estrane-3β,17β-diol (XVIIIa) m.p. 163–166°, raised by several crystallizations from ethanol–water to 171–173°, $[\alpha]_D^{26}$ +26°.[25] (Found: C, 77·8; H, 10·6. $C_{18}H_{30}O_2$ requires: C, 77·7; H, 10·9%).

5α-Estrane-3,17-dione (XVI). Oxidation of either XVa or XVIIIa with chromium trioxide reagent in the usual manner gave 5α-estran-3,17-dione. Recrystallization from Skellysolve B afforded an analytical sample m.p. 73–75°, $[\alpha]_D^{25}$ +139°.[26] (Found: C, 79·0; H, 9·5. $C_{18}H_{26}O_2$ requires: C, 78·8; H, 9·5%).

Raney nickel reduction of 5α-estrane-3,17-dione. 5α-Estran-3,17-dione (4·2 g) was dissolved in ethanol (300 ml) and refluxed with aged W-2 Raney Nickel catalyst as described above. Chromatography of the residue on silica gel (400 g) gave upon elution with benzene–ethyl acetate (10%) 5α-estran-3α-ol-17-one (XVIIb), m.p. 170–171·5°, $[\alpha]_D^{25}$ +115° (reported[11] m.p. 148°/164·5–167°, $[\alpha]_D^{21\cdot7}$ +110°) after crystallization from ethanol–water. (Found: C, 77·9; H, 9·9. Calc. for $C_{18}H_{28}O_2$: C, 78·2; H, 10·2%). Further elution with the same solvent system afforded the more polar 5α-estran-3β-ol-17-one (XVIIa). Crystallization from acetone–Skellysolve C gave an analytical sample, m..p. 181·5–184°, $[\alpha]_D^{25}$ +106° (reported[12] m.p. 177–179°, $[\alpha]_D^{20}$ +108°. (Found: C, 78·5; H, 10·2. Calc. for $C_{18}H_{30}O_2$: C, 78·2; H, 10·2%).

Raney nickel reduction of 5α-estran-17β-ol-3-one. Reduction of 5α-estran-17β-ol-3-one with aged

[24] Rapala and Farkas[7] reported the preparation of 5β-estran-3β,17β-diol by sodium borohydride reduction of the 3,17-diketone. Their physical constants (m.p. 202–204°, $[\alpha]_D$ +7·2°), however, are different from those obtained in this laboratory.

[25] This product has been reported as the solvate with two moles of acetone, m.p. 168–170°, $[\alpha]_D$ +16°.[10]

[26] This product agrees with that described by Chen[6] (m.p. 70°, $[\alpha]_D^{23\cdot5}$ +127·3° [acetone]) to which the 5β configuration was assigned.

W–2 Raney Nickel catalyst as described above gave a mixture of the C—3 epimeric diols. Chromatography on silica gel and elution with benzene–ethyl acetate (20%) gave 5α-estran-3α,17β-diol (XIXa) m.p. 187–192°, raised by recrystallization from ethyl acetate to 191·5–193°, $[\alpha]_D^{25}$ +31·5 (reported[11] m.p. 191–193°, $[\alpha]_D^{21\cdot1}$ +23·7°). (Found: C, 77·7; H, 10·4. Calc. for $C_{19}H_{30}O_2$: C, 77·7; H, 10·9%). This product was also obtained by reduction of XVIIb with sodium borohydride. Further elution with the same solvent system afforded the epimeric 5α-estrane-3β,17β-diol (XVIIIa) identical with that described above.

5α-Estran-17β-ol-3-one acetate (XVb). A solution of 5α-estran-17β-ol-3-one (5·0 g) in pyridine (25 ml) and acetic anhydride (5 ml), was allowed to stand at room temperature overnight and then poured slowly into ice-water. The resulting precipitate was removed by filtration and washed with 2 N hydrochloric acid, 2·5% sodium carbonate solution, and water. Recrystallization from Skellysolve C afforded 5α-estran-17β-ol-3-one acetate m.p. 103–105°. An additional recrystallization from methanol–water gave an analytical sample, m.p. 104–106°, $[\alpha]_D^{25}$ +47°.[37] (Found: C, 75·3; H, 9·4. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%). Recrystallization from absolute methanol gave the dimethyl ketal, m.p. 135–137°, $[\alpha]_D^{25}$ +20°. (Found: C, 72·5; H, 9·9. $C_{22}H_{36}O_4$ requires: C, 72·5; H, 10·0%).

Raney nickel reduction of 5α-estran-17β-ol-3-one acetate. 5α-Estrane-17β-ol-3-one acetate (XVb, 2·0 g) was dissolved in ethanol (150 ml) and refluxed for 2 hr with aged W–2 Raney Nickel catalyst (5·0 g) as described above. Adsorption of the residue on silica gel (200 g) and elution with benzene–ethyl acetate (5%) gave starting material (0·79 g) followed by 5α-estrane-3α,17β-diol 17-monoacetate (XIXb, 0·50 g), m.p. 163–167°. Recrystallization from acetone–Skellysolve C gave an analytical sample, m.p. 166–167°, $[\alpha]_D^{25}$ +18°. (Found: C, 74·6; H, 9·8. $C_{20}H_{32}O_3$ requires: C, 74·9; H, 10·1%). Further elution produced the epimeric 5α-estrane-3β,17β-diol 17-monoacetate (XVIIIb, 0·33 g) which upon crystallization from Skellysolve C afforded an analytical sample, m.p. 121–121·5°, $[\alpha]_D^{25}$ +15°. (Found: C, 74·8; H, 10·0. $C_{20}H_{32}O_3$ requires: C, 74·9; H, 10·1%).

5α-Estrane-3β,17β-diol diacetate (XXa). Acetylation of 5α-estrane-3β,17β-diol with acetic anhydride–pyridine at room temperature gave the corresponding diacetate (XXa). Crystallization from Skellysolve B gave an analytical sample, m.p. 142–145°, $[\alpha]_D^{25}$ +5°. (Found: C, 72·9; H, 9·5. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α-Estrane-3α,17β-diol diacetate (XXb). Acetylation of 5α-estrane-3α,17β-diol (0·4 g) was accomplished by warming on the steam bath for 2 hr with pyridine (9 ml) and acetic anhydride (1 ml). Work up in the usual manner and crystallization from ethanol afforded needles, m.p. 142–143·5°, $[\alpha]_D^{26}$ +24°. (Found: C, 72·9; H, 9·5. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

Acknowledgements—I am indebted to Dr. Frank B. Colton for many valuable discussions, to Dr. E. G. Daskalakis and his staff for their assistance in chromatography, to Mr. W. M. Selby and his group for performing most of the catalytic hydrogenations, and to Dr. F. J. Saunders of our Endocrinology Divisions for furnishing the biological data.

[37] This product agrees with the acetate described by Chen[6] m.p. 102–103° $[\alpha]_D^{22\cdot5}$ +39° (acetone) to which the 5β configuration was assigned.

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THE TRITERPENES OF COMMIPHORA—II

THE STRUCTURES OF COMMIC ACID C AND COMMIC ACID D

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Abstract—Evidence is presented to show that commic acid C is probably 2β,3β-dihydroxyolean-12-ene-23-oic acid (I); commic acid D is shown to be the ursane analogue, 2β,3β-dihydroxyurs-12-ene-23-oic acid (II).

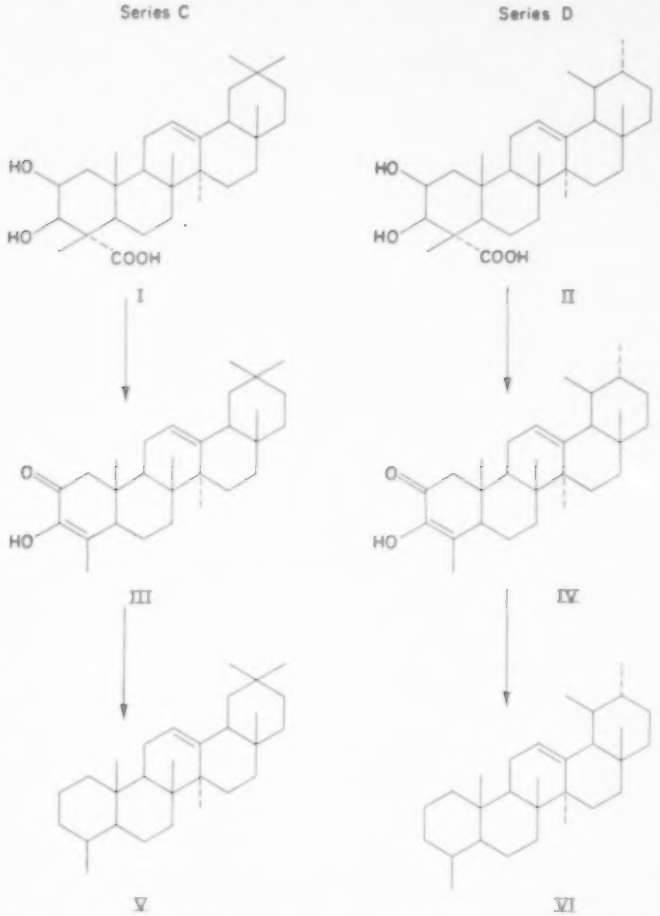
THE isolation of triterpene acids from *Commiphora pyracanthoides* Engl. (= *C. glandulosa* Schinz[2]) has been described in part I of this series, where it was also shown that methyl commates C and D were esters having two hydroxyl groups and one double bond.[3]

Both methyl commate C and D form isopropylidene derivatives, and both react with one equivalent of periodic acid, so that the two hydroxyl groups must be present in a *cis*-oriented α-glycol. Hydrolysis of the methyl esters occurs with surprising ease, suggesting that the carboxyl group, if tertiary, is in an equatorial position, though some reservation must be made in the light of the fact that the presence of a β- or γ-hydroxyl group can affect the ease of hydrolysis of methyl esters.[4] Neither acid formed a lactone, and only commic acid C crystallized, thus providing an excellent method of separating it from traces of commic acid D by recrystallization from methanol. It is interesting that halolysis of diacetyl methyl commate C with lithium iodide in dry lutidine[5] was found to give a good yield of commic acid C, a repetition of the experiment of Eschenmoser *et al.* using acetyl methyl oleanolate yielding almost pure acetyl oleanolic acid as they report.[6] The acids were oxidized with chromic acid in acetone solution, and the resulting ketoacids not isolated but treated directly with base, when compounds were obtained that gave a blue-green colour with ferric chloride, and had infra-red and ultra-violet spectra typical of diosphenols with oxygens at C-2 and C-3. The diosphenol from commic acid C was not identical with that from acid D, and their acetates were also clearly different, so that the difference between the two acids must lie in the carbon skeleton. The loss of carbon dioxide on diosphenol formation shows that the acids have hydroxyl groups at the β- and γ-positions to the carboxyl group.

Commic acid C is most probably a derivative of olean-12-ene, as was shown by the reaction of diacetyl methyl commate C with selenium dioxide in acetic acid, when a product was obtained displaying the ultra-violet triple absorption maxima associated with the oleana-11,13(18)-dienes. In a similar experiment diacetyl methyl commate D failed to react, so acid C was allocated structure I, while acid D was

[1] Present address: Chemin del 'Esplanade, Vernier, Genève, Switzerland.
[2] H. Wild, *Bol. da Sociedade Broteriana* [Série 2] **33**, 67 (1959). I am indebted to Dr. H. Hürlimann, CIBA, Basle, Switzerland, for drawing my attention to this reference.
[3] A. F. Thomas and J. M. Müller, *Experientia* **62**, 16 (1960).
[4] C. Djerassi and J. S. Mills, *J. Amer. Chem. Soc.* **80**, 1236 (1958).
[5] E. Taschner and B. Liberek, *Rocz. Chem.* **30**, 323 (1956).
[6] F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **43**, 113 (1960).

placed in the urs-12-ene series (structure II) and the diosphenols were ascribed structures III and IV respectively. The diosphenols were reduced by the Wolff-Kishner method, when C_{29} hydrocarbons were obtained (V and VI) respectively, the



one derived from commic acid D (II) having the properties reported for 23-norolean-12-ene (VI).[8] This hydrocarbon obtained from commic acid D was found to be identical with the C_{29} hydrocarbon produced by the Wolff-Kishner reduction of nor-β-boswellinone,[9] so commic acid D is therefore a 2,3-dihydroxyurs-12-ene-23(or 24)-oic acid. The corresponding hydrocarbon in the oleanene series is not known, so a direct comparison was not possible, but in view of the similarity between the derivatives of acid C and acid D, especially in their molecular rotational differences, the formulation of commic acid C as the corresponding 2,3-dihydroxyolean-12-ene-23(or 24)-oic acid seems justified.

The occurrence of 2α,3α-dihydroxy-triterpenes has not been observed,[7] and an

[7] C. Djerassi, D. B. Thomas, A. L. Livingstone and C. R. Thompson, *J. Amer. Chem. Soc.* **79**, 5292 (1957).
[8] L. Ruzicka, O. Jeger and W. Ingold, *Helv. Chim. Acta* **27**, 1859 (1944).
[9] I am indebted to Dr. T. G. Halsall for a generous sample of nor-β-boswellinone.

attempt was made to confirm the nature of the glycol as 2β,3β by measuring the rate of oxidation with lead tetraacetate in acetic acid.[10] The results were unsatisfactory, both methyl commate C and D being oxidized very slowly. Since no substance suitable for comparison was available, it was felt that these measurements were not reliable, and that the 2β,3β-conformation for the hydroxyl groups—and therefore, in view of the resistance to lactonization by the acids, the positioning of the carboxyl at C–23—represents the most plausible conformation for both acids.

In the case of methyl commate C, some experiments were undertaken with a view to attacking one of the hydroxyl groups preferentially, and though they were not pursued further, they will be briefly described. Methyl commate C formed a monoethylcarbonate very easily (incidentally supporting the assignment of the glycol with one axial and one equatorial hydroxyl group) but attempted oxidation of this with chromic–pyridine complex yielded only starting material—as, indeed, did every experiment in this series using this reagent. Methyl commate C does not form a *p*-toluenesulphonate, and methylsulphonyl chloride in pyridine yields only a dimethylsulphonate, reduction of which with lithium aluminium hydride gave a mixture of diols and triols from which only commol C[3] could be isolated with any certainty.

EXPERIMENTAL

M.p.s. are corrected. Rotations were measured at concentrations of 1% in chloroform. Alumina for chromatography was Woelm, neutral, grade III.

Commic acid C. Methyl commate C[3] (5 g) was heated under reflux with methanol (200 ml) and potassium hydroxide (20 g). After about 15 min the potassium salt of the acid began to crystallize, and after 4 hr no ether-soluble material could be isolated from the mixture. The salt was removed on a sinter and converted to *commic acid* C with methanol-conc hydrochloric acid; after crystallization from methanol, this had m.p. 343–345° (evac. tube). It was insufficiently soluble in chloroform, alcohol, dioxan or pyridine for its optical rotation to be measured in these solvents. (Found: C, 76·0; H, 10·2. $C_{26}H_{44}O_4$ requires: C, 76·2; H, 10·2%.) λ_{max}^{Nujol} 5·86 μ, unchanged after treatment with conc. sulphuric acid–dioxan.

In another experiment, diacetyl methyl commate C[3] (0·9 g) was heated in dry 2,6-lutidine with anhydrous lithium iodide (1·4 g) under nitrogen for 7 hr then worked up as described by Eschenmoser *et al.*[6] to give commic acid C, identical in all respects with that described above. Methylation of this sample with diazomethane in ether resulted in methyl commate C, identical with previously described material.

Commic acid C reacted with one equivalent of periodic acid in dioxan solution.

Reaction of methyl commate C with acetone. The resin from *C. pyracunthoides* was worked up as described previously[3] to the point at which the crude ester mixture was obtained after methylating the crude acids with diazomethane. Crystallization of this several times from chloroform removed most of the methyl commate D and E (see below), and the remainder (5 g) was allowed to stand at room temp. overnight with acetone (100 ml) and conc sulphuric acid (2 ml). The reaction mixture was poured into excess saturated sodium carbonate solution, and the product isolated with ether and chromatographed. Crystals (1 g) were eluted with benzene at first, but later fractions gave resins that appeared to be mixtures of the isopropylidene derivatives of methyl commates C and D and which crystallized only with difficulty. The first fractions, crystallized from methanol, had m.p. 168–169, $[\alpha]_D^{15°}$ + 65° (Found: C, 77·0; H, 10·2. $C_{34}H_{52}O_4$ requires: C, 77·5; H, 10·3%). Some difficulty was experienced in drying this sample. Hydrolysis of the isopropylidene derivative with methanol–conc hydrochloric acid yielded methyl commate C, identical in all respects with the ester previously described.[3]

Reaction of diacetyl methyl commate C with selenium dioxide. Diacetyl methyl commate C[3] (0·2 g) and selenium dioxide (0·2 g) were heated under reflux in glacial acetic acid (30 ml) for 2 hr, then poured into water and the product isolated with ether. The ether was washed with sodium

[10] C. Djerassi and R. Erlich, *J. Org. Chem.* **19**, 1351 (1954).

bicarbonate, and the residue after evaporation chromatographed. Benzene–light petroleum (9:1) eluted a substance, which, after crystallization from light petroleum had m.p. 157–159°, $[\alpha]_D^{19°}$ −38° (Found: C, 73·9; H, 9·3. $C_{35}H_{52}O_6$ requires: C, 73·9; H, 9·2%) λ_{max}^{EtOH} 240, 251, 260 mμ ε 14,800, 11,600, 6,800 respectively, $\lambda_{max}^{CS_2}$ 13·17 μ (*cis*-disubstituted double bond).

Treatment of methyl commate D in the same way yielded only unchanged starting material.

Diosphenol C (III). Commic acid C (0·25 g) was suspended in acetone (100 ml) and treated dropwise at room temp over 30 min with chromic oxide in sulphuric acid and water (0·4 ml of a mixture from 2·67 g CrO_3, 2·3 ml. conc H_2SO_4 and 7·7 ml water) when it was poured into water (500 ml). The product, isolated as usual with ether, was heated under reflux for one hr with potassium hydroxide in methanol (10%, 10 ml). Dilution with water and acidification with hydrochloric acid enabled the product to be isolated with ether. It was chromatographed, and elution with benzene and crystallization from methanol gave *diosphenol* C, m.p. 228–230°, $[\alpha]_D^{20°}$ +132° (Found: C, 81·9; H, 10·4. $C_{29}H_{44}O_2$ requires: C, 82·0; H, 10·4%). λ_{max}^{EtOH} 281 mμ ε 9,000; $\lambda_{max}^{EtOH-KOH}$ 329 mμ, ε 3,500. $\lambda_{max}^{CH_2Cl_2}$ 2·90, 5·99, 6·08 μ.

Diosphenol C acetate. This was prepared from acetic anhydride in pyridine and crystallized from methanol, m.p. 220–221°, $[\alpha]_D^{20°}$ +156° (Found: C, 79·7; H, 9·9. $C_{31}H_{46}O_3$ requires: C, 79·8; H, 9·9%). $\lambda_{max}^{CHCl_3}$ 5·67, 5·95, 6·07 μ, λ_{max}^{EtOH} 250 mμ, ε 7,900.

Wolff-Kishner reduction of diosphenol C (*23-norolean-12-ene*). Diosphenol C (80 mg), diethylene glycol (15 ml), ethanol (15 ml) and hydrazine hydrate (10 ml) were heated under reflux together for 15 min. Potassium hydroxide (5 g) was added and the mixture concentrated by distillation until the temperature attained 200–220°, where it was maintained for 3 hr. The mixture was poured into water and the product isolated with pet ether. The petroleum solution was filtered through alumina and the product obtained on evaporation was crystallized from acetone, m.p. 150°, $[\alpha]_D^{20°}$ +106° (Found: C, 87·7; H, 12·2. $C_{29}H_{48}$ requires: C, 87·8; H, 12·2%).

It was found that Clemmenson reduction of diosphenol C using zinc amalgam (made from 10 g zinc wool and 0·75 g mercuric chloride), glacial acetic acid (20 ml) and conc hydrochloric acid (4 ml) heated for 20–30 min gave a good yield of the same 23-norolean-12-ene. Longer periods of reflux (over 2 hr) yielded mostly non-crystalline material.

Ethoxycarbonyl methyl commate C. This was made by dissolving the triterpene ester (0·5 g) in dioxan (10 ml) and pyridine (1·6 ml) at 0° and adding dropwise ethyl chloroformate (2 ml). After 2 hr the mixture was diluted with water and the product isolated with ether. Chromatography on alumina gave first, a small amount of gum (eluted with benzene) with no I.R. absorption between 2·5–3·0 μ, then the *ethoxycarbonyl* derivative which was crystallized from 90% methanol to m.p. 196–198°, $[\alpha]_D^{21°}$ +38° (Found: C, 73·1; H, 9·7. $C_{34}H_{54}O_6$ requires: C, 73·1; H, 9·7%). $\lambda_{max}^{CHCl_3}$ 2·93 (v. broad), 5·81 μ.

Dimethylsulphonyl methyl commate C. This was prepared with methyl sulphonyl chloride in pyridine, and after chromatography on alumina (eluted with benzene), crystallized from ethanol–pet ether, m.p. 222–224° $[\alpha]_D^{20°}$ +41°, (Found: C, 62·1; H, 8·6; S, 10·0. $C_{33}H_{54}O_6S_2$ requires: C, 61·7; H, 8·5; S, 10·0%). $\lambda_{max}^{CHCl_3}$ 5·78, 8·47 μ, no band at 2·5–3·0 μ.

Treatment with sodium iodide in acetone[11] left this compound unchanged.

Commic acid D. This was prepared by hydroiysis of the methyl ester with potassium hydroxide in methanol exactly as described for commic acid C. Commic acid D did not crystallize, but had λ_{max}^{nujol} 5·86 μ, unchanged after treatment with conc sulphuric acid–dioxan.

Methyl commate D reacted with one equivalent of periodic acid in dioxan solution.

Isopropylidene methyl commate D. This was most easily obtained by treatment of the part of the crude ester mixture that was insoluble in chloroform with acetone–sulphuric acid (2%) as described for the isopropylidene derivative of methyl commate C. Chromatography of the product yielded on elution with benzene *isopropylidene methyl commate* D, which, after crystallization from methanol had m.p. 153–154°, $[\alpha]_D^{19°}$ +88° (Found: C, 77·3; H, 10·2. $C_{34}H_{54}O_6$ requires: C, 77·5; H, 10·3%). $\lambda_{max}^{CHCl_3}$ 5·79 μ.

Continued elution of the column with benzene–ether (1:1) yielded a substance subsequently shown to be *isopropylidene methyl commate* E, since hydrolysis with methanol–conc hydrochloric acid yielded methyl commate E.[8] Crystallization from methanol gave leaflets of m.p. 240–241°, $[\alpha]_D^{20°}$ +53° (Found: C, 75·1; H, 10·0. $C_{34}H_{54}O_5$ requires: C, 75·2; H, 10·0%). $\lambda_{max}^{CH_2Cl_2}$ 2·77, 5·78, 9·57, 11·66 μ.

[11] H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 3749 (1959).

The isopropylidene methyl commate D obtained in this experiment was hydrolysed to methyl commate D with methanol–conc hydrochloric acid.

Diosphenol D (IV). This was obtained in a manner completely analogous to that described above for diosphenol C. After chromatography and crystallization from methanol, diosphenol D had m.p. 233–235° (admixture with diosphenol C, m.p. 180–185°) $[\alpha]_D^{19°}$ +150° (Found: C, 81·8; H, 10·6. $C_{29}H_{44}O_2$ requires: C, 82·0; H, 10·4%). λ_{max}^{EtOH} 282 mμ, ε 13,800, $\lambda_{max}^{EtOH-KOH}$ 329 mμ, ε 9,500. $\lambda_{max}^{CH_2Cl_2}$ 2·90, 5·99, 6·08 μ.

Diosphenol D *acetate*. This, made with acetic anhydride in pyridine and crystallized from methanol had m.p. 210–212°, $[\alpha]_D^{18°}$ +156° (Found: C, 79·8; H, 9·8. $C_{31}H_{46}O_3$ requires: C, 79·8; H, 9·9%). λ_{max}^{EtOH} 250 mμ, ε 8,500; $\lambda_{max}^{CHCl_3}$ 5·66, 5·98, 6·08 μ.

23-*Norurs*-12-*ene*. A. From Diosphenol D. The Wolff–Kishner reduction was carried out exactly as described above for diosphenol C, yielding a product of m.p. 172–173° $[\alpha]_D^{20°}$ +106°.

B. Similar treatment of nor-β-boswellinone[9] yielded 23-norurs-12-ene of identical m.p. and mixed m.p. On admixture with the compound obtained by Wolff–Kishner reduction of diosphenol C, the m.p. was found to be 120–125°.

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THE STRUCTURE OF δ-CADINOL[1]

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(*Received* 13 *April* 1961)

Abstract—Albicaulol, a crystalline cadinol isolated from the oleoresin of *Pinus albicaulis* and *Pinus armandi*, has been found to be identical with δ-cadinol. The structure of δ-cadinol has been shown to be Δ^{6}-cadinene-3-ol rather than the Δ^{9}-structure assigned by Motl, Sýkora, Herout and Šorm.

IN the course of an investigation of the composition of gum terpentines of pine trees, Haagen-Smit, Wang and Mirov[2] isolated a crystalline sesquiterpenic alcohol (m.p. 135°) from the heavy oil fraction of *Pinus albicaulis*. The same alcohol was also found to occur in the oleoresin of *Pinus armandi*[3] and in the heartwood of *Chamaecyparis lawsoniana*.[4] The compound was called "albicaulol" and was shown to possess the formula $C_{15}H_{26}O$ and to have a tertiary hydroxyl group. Through the kind cooperation of Dr. Mirov, a supply of oleoresin from *P. armandi* was made available to us and the structural studies related to albicaulol were initiated.

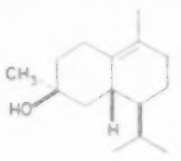
Albicaulol (V) upon dehydrogenation over 5 per cent palladium-on-carbon yielded cadalene, identified as the trinitrobenzoate and picrate, and upon reaction with hydrogen chloride yielded (−)-cadinene dihydrochloride. The presence of one olefinic linkage was established by hydrogenation of V to a saturated dihydro derivative. As was reported by the earlier workers,[2] the hydroxyl function appeared to be tertiary since most esterification attempts returned only starting material and only when forcing conditions (acetic anhydride at 140°) were used was an acetate obtained. The presence of one double bond, a tertiary hydroxyl function and a cadinene nucleus indicated that albicaulol possessed a cadinol structure.

Of the twelve theoretically possible cadinols which can give rise to (−)-cadinene dihydrochloride, only three isomers have been found in nature, α-cadinol,[5–7] δ-cadinol,[7–9] and a cadinol of m.p. 78°.[7] Upon comparison of the physical and spectral properties of albicaulol with those of δ-cadinol, it appeared that the materials were identical. The finding of no depression of melting point of a mixture of the two compounds clearly established their identity.[10] The Czech workers have reported[7,8] the structure of δ-cadinol to be I. The location of the double bond was suggested on the basis of infrared spectroscopy and on the basis that δ-cadinol upon ozonization

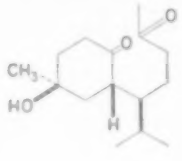
[1] This work was supported in part by the National Science Foundation, Grant G-6212.
[2] A. J. Haagen-Smit, T. H. Wang and N. T. Mirov, *J. Amer. Pharm. Assoc.* (*Sci. Ed.*) **40**, 557 (1951).
[3] N. T. Mirov and P. M. Iloff, Jr., *J. Amer. Pharm. Assoc.* (*Sci. Ed.*) **44**, 424 (1955).
[4] G. Kritchevsky and A. B. Anderson, unpublished results.
[5] P. A. Plattner and R. Markus, *Helv. Chim. Acta* **25**, 1674 (1942).
[6] G. Kritchevsky and A. B. Anderson, *J. Amer. Pharm. Assoc.* (*Sci. Ed.*) **44**, 535 (1955).
[7] O. Motl, V. Sýkora, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **23**, 1297 (1958).
[8] V. Herout and V. Sýkora, *Tetrahedron* **4**, 246 (1958).
[9] H. Erdtman, Z. Pelchowicz and J. G. Topliss, *Acta Chim. Scand.* **10**, 1563 (1956).
[10] We are indebted to Professor H. Erdtman for kindly performing this comparison.

yielded a diketo-alcohol which was assigned structure II since the latter material lacked aldehydic properties.

In the course of our preliminary work with albicaulol (now δ-cadinol) it was found that the nuclear magnetic resonance spectrum clearly indicated the presence of one vinyl proton (4·43 τ).[11] This conclusion that a trisubstituted double bond was present



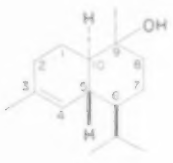
I



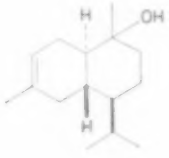
II

was verified when it was found that δ-cadinol upon oxidation with potassium permanganate gave a dihydroxy ketone VI in 59 per cent yield. In order to establish further the identity of our material with that of the Czech workers, the cadinol was osmylated and there was obtained a triol (VII) possessing identical properties with those reported for a similar triol prepared by Motl, Sýkora, Herout and Šorm from δ-cadinol.[7] Repetition of their ozonation experiment, however, failed to yield any crystalline material, and hence evaluation of this important reaction was not possible.

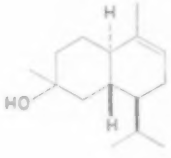
With the present evidence it must be concluded that δ-cadinol possesses a tri- and not a tetra-substituted double bond. Since the alcohol yielded (−)-cadinene dihydrochloride, δ-cadinol must possess the structure III, IV or V (disregarding the stereochemistry of the hydroxyl group).* The structure III can be ruled out on the basis of



III



IV



V

the spin-spin coupling pattern shown by the vinyl proton of the double bond in its NMR spectrum. It was possible to study a closely related model of III since α-cadinol possesses a similar structure, the difference being due to the stereochemistry of the hydroxyl group.[7,12] The NMR spectrum of α-cadinol[13] showed only a singlet (4·52 τ) for the vinyl proton. This finding of a singlet required further consideration since a doublet might have been expected. By examination of a molecular model it is seen that the proton at the ring juncture (C_5) is approximately at a 90° angle to the vinyl proton and when the dihedral angle of two protons which couple is about 90°, the coupling constant is about zero.[14] By consideration of the dihedral angle between the vinyl

* The numbering of the cadinene nucleus is that normally used for a steroid and differs from the numbering system suggested by Motl, Sýkora, Herout and Šorm.[7]

[11] Originally, Erdtman[9] attributed the absorption at 873 cm^{-1} to a trisubstituted double bond whereas Šorm and his co-workers believed this band was out of the normal range for such a structure.

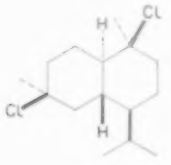
[12] M. D. Soffer, M. Brey and J. Fournier, *Chem. & Ind.* 19 (1958).

[13] Kindly determined by the Stanford Research Institute.

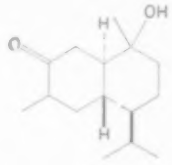
[14] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

proton and the quasi-equatorial and the quasi-axial protons on the adjacent carbon, C_1 in IV and C_7 in V, a doublet would be expected. The NMR spectrum of δ-cadinol[13] showed the vinyl proton as a doublet ($J = 6{\cdot}5$ c/s). Thus, in view of the different NMR spectra of α- and δ-cadinol, it can be concluded that III cannot represent the formulation of δ-cadinol.

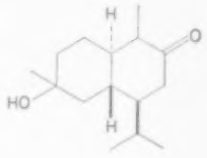
To differentiate between IV and V, the position of the double bond must be located. The usual method of locating such a bond in a cadinene molecule is to insert a methyl group (via epoxidation and Grignard reactions) on the tertiary end of the double bond and to dehydrogenate the resulting material to a methylcadalene.[7,12] However, since the absolute configuration of (−)-cadinene dihydrochloride (VIII) recently has been established,[15] it is possible to employ optical rotatory dispersion measurements to locate the double bond. In the formation of the dihydrochloride VIII from δ-cadinol, the configurations of C_5, C_6 and C_{10} are not affected, and these centers possess the same absolute configuration in δ-cadinol as in VIII. The transformation of the lesser substituted end of the trisubstituted double bond to a carbonyl group, such as in IX or X, would permit the position of the unsaturation to be located since the rotatory dispersion curve of IX should show a negative Cotton effect[16] and X a positive Cotton effect.[17]



VIII



IX



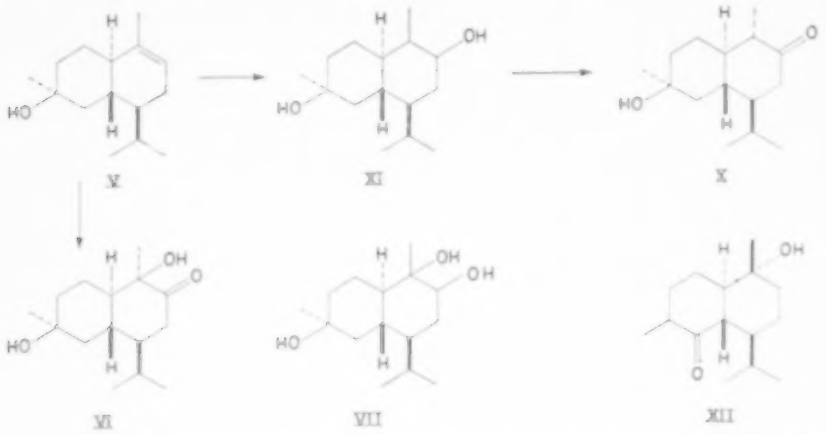
X

Of the various methods available for the conversion of δ-cadinol (V) to a saturated hydroxyketone, the method of choice is hydroboration followed by oxidation. With the hydroboration reaction it is possible to add the equivalent of water to a double bond in an anti-Markownikoff fashion.[18] When δ-cadinol was allowed to react with diborane in diglyme followed by oxidation with hydrogen peroxide the diol XI was obtained in 35 per cent yield. Oxidation of XI with chromic acid yielded the hydroxyketone, X, in 45 per cent yield. The optical rotatory dispersion curve of X showed a positive Cotton effect,[19] establishing the structure of the material as shown. It must be concluded that δ-cadinol possesses the structure V. Although no definite proof is on hand, we agree with the previous workers[7] that the hydroxyl group is most likely axial since it is so difficult to esterify.

The optical rotatory dispersion curve of the dihydroxyketone VI was found to be of a negative Cotton type.[19] This change in sign upon making C_9 fully substituted is expected on the basis of the Octant Rule[20] since a strongly contributing axial group falls into a negative octant. This finding of a negative curve is additional support for the location of the double bond since although the ketone XII derived from an

[15] V. Sýkora, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **23**, 2181 (1958).
[16] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); C. Djerassi, *Optical Rotatory Dispersion* pp. 42, 175. McGraw-Hill, New York (1960).
[17] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* **78**, 3163 (1956).
[18] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **81**, 6428 (1959).
[19] We are indebted to Professor C. Djerassi for this determination.
[20] The use of this rule is summarized in ref. 16, p. 181.

α-cadinol type structure possesses a positive Cotton curve[7,8] as does X, an axial substituent on C_3 falls into a positive octant and no change in sign would be expected. From this dispersion curve of VI it also was possible to assign an axial configuration to the C_9-hydroxyl group in that the position of the first extremum of the dispersion



curve was shifted bathochromically 15 mμ from that of the related ketone X. Such a shift has been shown to be characteristic for an axial hydroxyl group adjacent to a ketone.[21]

In view of the revised structure for δ-cadinol it is suggested that the trivial name no longer be employed since it was only assigned to the compound on the basis that it did possess a tetrasubstituted double bond corresponding to a similar bond in δ-cadinene.

EXPERIMENTAL[22]

Isolation of δ-cadinol (albicaulol). A 5 gal sample of oleoresin collected from *Pinus armandi* was supplied by the Mutual Security Agency, Taipei, Formosa.[23] The oleoresin was processed as described by Mirov and Iloff[3] and from the heavy oil fraction 8·7 g of δ-cadinol was obtained, m.p. 138–139°, $[\alpha]_D^{23}$ −102·3° (*c*, 3·2, EtOH).

(Found: C, 80·86; H, 12·11. Calc. for $C_{15}H_{26}O$ (222·36): C, 81·02; H, 11·79.)

Cadalene from δ-cadinol. A mixture of 520 mg of δ-cadinol and 110 mg of 5% palladium-on-carbon was heated in a bath at 210–220° for 4 hr. After the mixture had cooled to room temperature, 10 ml of 95% ethanol was added, the mixture refluxed for 10 min, the catalyst filtered and the filtrate concentrated to about 3 ml. To 0·5 ml of the ethanolic solution there was added 3 ml of a saturated ethanolic solution of 1,3,5-trinitrobenzene. The solution was warmed on a steam-bath for 2 min and allowed to stand at 0° for 6 hr. The yellow-orange needles of cadalene trinitro benzoate which formed were collected, washed with cold ethanol and dried, m.p. 110–111°, no depression upon admixture with an authentic sample.[24]

To a 1 ml portion of the ethanol solution from the dehydrogenation there was added 1 ml of a saturated ethanol solution of picric acid and the reaction processed as above to yield cadalene picrate, m.p. 114–115°, no depression upon admixture with authentic sample.[24]

(−)-Cadinene dihydrochloride from δ-cadinol. A solution of 111 mg of δ-cadinol in 15 ml of anhydrous ether was saturated with anhydrous hydrogen chloride at 5° and the solution kept at that

[21] C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta* **41**, 250 (1958).
[22] Analyses performed by the Microanalytical Laboratory, College of Chemistry, University of California.
[23] We are indebted to Dr. Hubert G. Schenk and Mr. Paul Zengraff of the Mutual Security Agency for their assistance in procuring the oleoresin sample.
[24] Kindly supplied by Dr. P. M. Iloff, Jr.

temperature for 24 hr. The solvent was removed and the dark red viscous residue crystallized upon cooling to 0° and the product was recrystallized from methanol to yield 15 mg of colorless needles, m.p. 117–118°, no depression upon admixture with an authentic sample of (−)-cadinene dihydrochloride.[24]

Dihydro-δ-cadinol. A mixture of 111 mg of δ-cadinol, 1 g of W–2 Raney nickel and 10 ml of ethanol was hydrogenated at room temperature and 1200 lb/in² for 12 hr. The catalyst was filtered, washed thoroughly with ethanol and the filtrate concentrated under reduced pressure. The residue after chromatography on Woelm alumina (Act. I) yielded 71 mg of crude dihydro alcohol, m.p. 69–73°. The solid was fractionally sublimed to yield 49 mg (37%) of a dihydro-δ-cadinol, m.p. 76–77°. The ultraviolet spectrum showed virtually no end absorption, and the NMR spectrum showed no vinyl proton absorption.

(Found: C, 80·43; H, 12·68. Calc. for $C_{15}H_{28}O$ (224·37): C, 80·29; H, 12·58.)

A similar isomer has been obtained by Erdtman[9] along with higher melting materials.[7]

δ-Cadinol acetate. A solution of 111 mg of δ-cadinol, 82 mg of anhydrous sodium acetate and 5 g of redistilled acetic anhydride was heated at 145° for 3 hr. The excess acetic anhydride was removed under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with aqueous sodium bicarbonate, with water and dried. The ether was evaporated and the residual yellow oil chromatographed on Woelm alumina (Act. I) to yield 37 mg of a hydrocarbon, 48 mg of acetate and 4 mg of unreacted starting material. The acetate was rechromatographed and the center cuts were recrystallized from methanol–water (19:1), m.p. 45–46°.

(Found: C, 77·46; H, 10·81. Calc. for $C_{17}H_{28}O_2$ (264·39): C, 77·22; H, 10·67.)

Cadinane-3,9-diol-8-one (VI). To a solution of 111 mg of δ-cadinol in 25 ml of purified acetone cooled in an ice-bath there was added, dropwise with stirring, a solution of 630 mg of potassium permanganate in 10 ml of water. The solution was allowed to warm to room temperature and stirred at that temperature for 10 hr. At the end of this time the unreacted permanganate was destroyed with sodium bisulfite, the manganese dioxide filtered and the filtrate concentrated until all of the acetone was removed. The remaining alkaline aqueous solution was cooled to ice temperature, acidified with 1% hydrochloric acid and extracted with ether. The ethereal solution was washed with dilute sodium bicarbonate, with water and dried. The ether was evaporated and the residual solid recrystallized twice from benzene, yield 74 mg (59%), m.p. 143–144°.

(Found: C, 70·64; H, 10·11. Calc. for $C_{15}H_{26}O_2$ (254·36): C, 70·83; H, 10·30.)

The compound gave a positive test with periodic acid. The infrared spectrum of the material in chloroform showed the following bands: 3480 and 3340 cm^{-1} (hydroxyl), 1685 cm^{-1} (carbonyl). The optical rotatory dispersion of VI in methanol (*c*, 0·12) was as follows: $[\alpha]_{700}$ −10°, $[\alpha]_{589}$ −15°, $[\alpha]_{310}$ −170° (min), $[\alpha]_{272}$ +420° (max), $[\alpha]_{250}$ +370°; no change upon addition of acid.

Cadinane-3,8,9-triol (VII). A solution of 444 mg of δ-cadinol in 10 ml of dioxane containing three drops of pyridine was added to a solution of 650 mg of osmium tetroxide in 10 ml of dioxane and the resulting solution allowed to stand in the dark for 7 days. Hydrogen sulfide was bubbled into the solution for 15 min and the resulting black slurry filtered. The solid was washed with hot ethyl acetate and the combined filtrate concentrated to dryness. The residual thick oil (515 mg) was crystallized from benzene–petroleum ether to yield 448 mg of white needles, m.p. 147–157°, which was recrystallized twice from the same solvent pair, yield 361 mg (70·5%), m.p. 160·5–161·5° (lit.[7] m.p. 157°).

(Found: C, 70·10; H, 10·90. Calc. for $C_{15}H_{28}O_3$ (256·37): C, 70·27; H, 11·01).

The combined mother liquors upon concentration gave 38 mg of an isomeric triol, m.p. 139·0–140·0°. The product was recrystallized from benzene, m.p. 139·0–140·0, yield 25 mg (4·5%).

Cadinane-3,8-diol (XI). Following the procedure of Brown and Subba Rao[16], a solution of 630 mg of δ-cadinol in 10 ml of diglyme was allowed to react with 420 mg of sodium borohydride and 4·5 g of boron trifluoride etherate. After 1½ hr, the reaction mixture was hydrolyzed with ice-water. When hydrogen evolution ceased, 50 ml of 3 N sodium hydroxide was added and 2·5 ml of 30% hydrogen peroxide added dropwise. After 30 min the reaction mixture was poured into 200 ml of water and processed as usual. The residual oil partially crystallized on cooling. The solid was separated and the filtrate was dissolved in a small volume of ether and upon cooling more solid was deposited. Concentration of the ethereal solution yielded additional material. The combined solids were recrystallized from petroleum ether, yield 237 mg (35%), m.p. 126·5–127·5°.

(Found: C, 74·68; H, 11·63. Calc. for $C_{15}H_{28}O_2$ (240·37): C, 74·95; H, 11·74.)

Cadinane-3-ol-8-one (X). To a solution of 130 mg of cadinane-3,8-diol (XI) in 15 ml of glacial acetic acid there was added, dropwise with stirring, a solution of 40 mg of chromium trioxide in 0·2 ml of water and 0·3 ml of glacial acetic acid over a 5 min period. The resulting dark brown solution was diluted with 15 ml of water and extracted with benzene. The benzene extract was washed with sodium bicarbonate, with water and the solvent evaporated. The crystalline residue was recrystallized twice from petroleum ether, yield 59 mg (54%), m.p. 85·0–86·0°, ν_{max}^{KBr} 3420, 1695 cm^{-1}.

(Found: C, 75·70; H, 11·22. Calc. for $C_{15}H_{26}O_2$ (238·36): C, 75·58; H, 11·00.)

The optical rotatory dispersion of X in methanol (*c*, 0·08) was as follows: $[\alpha]_{700}$ +10°, $[\alpha]_{589}$ +25°, $[\alpha]_{295}$ +360° (max), $[\alpha]_{262}$ −110° (min).

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FRIEDELIN AND RELATED COMPOUNDS—V[1]

THE ACTION OF N-BROMOSUCCINIMIDE ON FRIEDELIN AND DERIVATIVES

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(*Received* 28 *April* 1961)

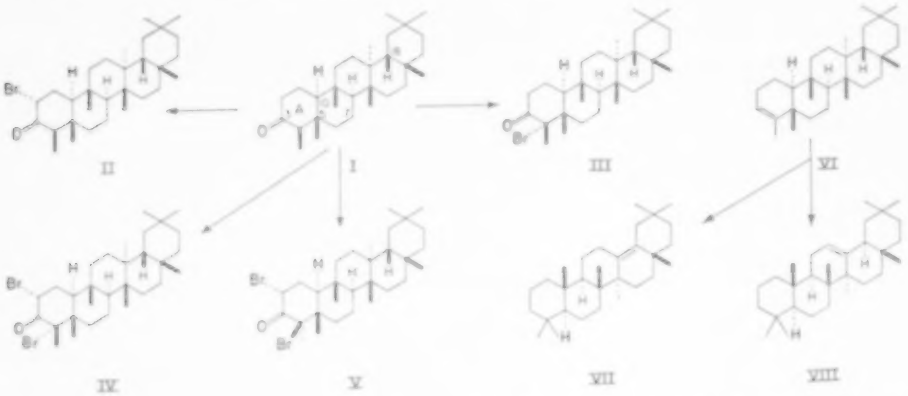
Abstract—Friedelin gives 4α-bromofriedelin on treatment with N-bromosuccinimide. 2α-Bromofriedelin, 4α-bromofriedelin and friedelane are preferentially oxidized to the corresponding Δ^{18}-olefins.

A STUDY of the bromination products of the pentacyclic triterpenoid ketone, friedelin (I), proved extremely valuable not only in revealing the structural detail of the terminal ring A but also in establishing the absolute configuration. Corey and Ursprung[2] showed that direct monobromination of friedelin gave 2α (axial)-bromofriedelin (II) and that the isomeric 4α (axial)-bromofriedelin (III) could be obtained by bromination of the appropriate enol benzoate. A more complex situation exists with regard to the preparation of the dibromoketones. A dibromofriedelin prepared in chloroform solution in the presence of hydrogen bromide showed an ultraviolet absorption maximum at 332 mμ, indicative of both bromine atoms having axial conformations, and has accordingly been regarded[2] as 2α:4α-dibromofriedelin (IV). A second dibromofriedelin, described by Djerassi and coworkers[3], and prepared by bromination of 2α-bromofriedelin in acetic acid, showed an ultraviolet absorption (310·5 mμ) indicative of one axial α-bromine atom and has been formulated as 2α:4β-dibromofriedelin (V), in agreement with rotatory dispersion data. A third isomer prepared by Takahashi and Ourisson[4] by dibromination of friedelin in chloroform–acetic acid shows an absorption inflection at 320 mμ. No structure has been assigned to this dibromoketone or an unstable tribromoketone also described by these workers. On experiencing difficulties in obtaining reproducible results by direct bromination of friedelin, we sought alternative methods and have examined the action of N-bromosuccinimide on friedelin and derivatives.

Treatment of friedelin (I) in carbon tetrachloride solution with a molar equivalent of N-bromosuccinimide gave, in excellent yield, 4α-bromofriedelin (III). Since 2α-bromofriedelin is isolated on direct bromination of friedelin this forms a marked contrast with the behavior of the 3-ketosteroids where, in both the cholestane and coprostane series, the same monobromination products are isolated by either procedure.[5] By treatment of 4α-bromofriedelin (III) with bromine in acetic acid solution, isomerization rather than further substitution occurred, and 2α-bromofriedelin (II) was isolated. As anticipated from this result, the 4α-bromoketone

[1] Part IV: R. Stevenson, *J. Org. Chem.* **26**, 2142 (1961).
[2] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.* **78**, 5041 (1956).
[3] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **80**, 1216 (1958).
[4] T. Takahashi and G. Ourisson, *Bull. Soc. Chim. Fr.* 353 (1956).
[5] C. Djerassi and C. R. Scholz, *Experientia* **3**, 107 (1947).

($[\alpha]_D$ +92°) is unstable in chloroform containing hydrogen bromide at room temperature, the presumed equilibrium mixture ($[\alpha]_D$ ca. −75°) being formed after 24 hr. Similar equilibration of 2α-bromofriedelin gave the same result.



Since this route for obtaining a dibromofriedelin was unsuccessful, the alternative method of treating 2α-bromofriedelin (II) with N-bromosuccinimide was examined. The isolated product was an unsaturated monobromo ketone, $C_{30}H_{47}OBr$, the presence of an ethylenic function being indicated by a positive tetranitromethane test. Examination of the ultraviolet and infrared spectra of this ketone showed the double bond was *not* conjugated to the carbonyl group and that the α-bromine atom retained an axial conformation. In view of the marked propensity of certain friedelin derivatives to undergo molecular rearrangement—the most notable example of which is probably the acid isomerization of friedel-3-ene (VI) to the mixture of olean-13:18-ene (VII) and 18α-olean-12-ene (VIII)[6,7]—it was considered that this non-conjugated bromoketone had probably arisen by a molecular rearrangement of a 2α:4-dibromoketone intermediate (or derived radical or cation) with elimination of hydrogen bromide. A precedent for such a postulated rearrangement is provided by the action of silver acetate on 4α-bromofriedelin (III) to yield a product[2] which was shown[8] to be a mixture of the non-conjugated ketones, alnus-5-enone (IX, R = H) and alnus-5(10)-enone (X, R = H). An interesting molecular rearrangement involving an 1:2-alkyl group shift under normal N-bromosuccinimide reaction conditions has been described.[9]

The possibility that the unsaturated bromoketone, $C_{30}H_{47}OBr$ derived from II could be represented as a 2-bromoalnusenone (IX, R = Br or X, R = Br) was

[6] G. Brownlie, F. S. Spring, R. Stevenson and W. S. Strachan, *J. Chem. Soc.* 2419 (1956).
[7] G. Brownlie, M. B. E. Fayez, F. S. Spring, R. Stevenson and W. S. Strachan, *J. Chem. Soc.* 1377 (1956).
[8] J. M. Beaton, F. S. Spring, R. Stevenson and J. L. Stewart, *Tetrahedron* **2**, 246 (1958).
[9] R. A. Barnes and G. R. Buckwalter, *J. Amer. Chem. Soc.* **73**, 3858 (1951) have shown that treatment of 1,1,6-trimethyl-1,2-dihydronaphthalene (A) with N-bromosuccinimide gave an allylic bromide which was aromatized to 1,2,6-trimethylnaphthalene (B) either by silver ion or heat (temperature of refluxing carbon tetrachloride).

(A) (B)

excluded, however, when it was established that the product $C_{30}H_{48}O$ obtained by zinc debromination in neutral solution differed from either alnusenone (IX, R = H and X, R = H).

When 4α-bromofriedelin (III) was treated with N-bromosuccinimide under conditions identical to those which the 2α-bromoketone (II) had been subjected, there was obtained a second isomeric non-conjugated axial bromosubstituted ketone, $C_{30}H_{47}OBr$ which yielded, however, the same debromination product, $C_{30}H_{48}O$. Since we regard this ketone, from the evidence described later, as having the constitution, friedel-18-en-3-one (XIII), the isomeric bromoketones obtained from II and III by the action of N-bromosuccinimide are assigned the structures, 2α-bromofriedel-18-en-3-one (XI) and 4α-bromofriedel-18-en-3-one (XII) respectively. It was established, furthermore, that the debromination of XI and XII to XIII had proceeded in the expected manner since ketone (XIII) regenerated the 4α-bromoketone (XII) on treatment with N-bromosuccinimide.

Reduction of the ketone (XIII) with lithium aluminum hydride gave in high yield an alcohol (XIV, R = H), further characterized as its acetate (XIV, R = Ac) and reduction by the Huang-Minlon method gave the unsaturated hydrocarbon (XV). Comparison of the specific rotation values (see Table 1) of the unsaturated ketones, produced by N-bromosuccinimide oxidation (and their derivatives) and the friedelin analogues shows such close correspondence as to suggest strongly that the former in fact possess a friedelane skeleton and not that of a rearranged skeleton. This conclusion is further supported by a comparison of the previously reported optical rotatory dispersion curves[3] of I, II and III (in dioxane solution) with their respective analogues XIII, XI and XII which agree well in the sign of the Cotton effect and the wavelength locations of peaks and troughs (see experimental).

Whereas the action of N-bromosuccinimide on the ketones (II) and (III) would be expected *a priori* to yield products which are dibromofriedelins, αβ-unsaturated

ketones or rearranged non-conjugated ketones, the circumstantial evidence provided by the rotation data indicate that the products are ethylenic non-conjugated friedelins and hence that attack has proceeded at a site not activated by the carbonyl group. In seeking chemical support for this conclusion, the action of N-bromosuccinimide on the saturated hydrocarbon, friedelane (XVI), was examined and from the reaction mixture the unsaturated hydrocarbon (XV), identical in all respects with that prepared by Huang-Minlon reduction of the ketone (XIII), was isolated. It remained, consequently to locate the site of the double bond introduced by the N-bromosuccinimide oxidation.

TABLE 1

	$[\alpha]_D$	
2α-Bromoketone (XI)	− 139°[a] − 140°[b]	2α-Bromofriedelin (II)
4α-Bromoketone (XII)	+ 87°[a] + 92°[b]	4α-Bromofriedelin (III)
Ketone (XIII)	− 28°[a] − 22°[b]	Friedelin (I)
Alcohol (XIV, R = H)	+ 25°[a] + 22°[b]	Friedelan-3β-ol
Acetate (XIV, R = Ac)	+ 30°[a] + 34°[b]	Friedelan-3β-ol acetate
Hydrocarbon (XV)	+ 17°[a] + 22°[b]	Friedelane (XVI)

[a] Values reported in experimental. [b] Values reported in ref. 6.

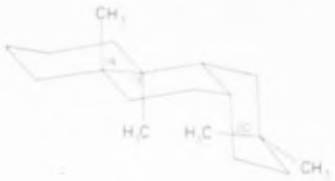
The unsaturated hydrocarbon (XV) resisted catalytic hydrogenation but yielded an oxide, $C_{30}H_{50}O$, on treatment with perbenzoic acid, indicating that the double bond has a degree of steric hindrance comparable to the Δ^{12}-trisubstituted ethylenic linkage in the β-amyrin series.[10] The terminal ultraviolet absorption of compounds (XIII), (XIV, R = H) and (XV) indicate that the double bond is tri-substituted,[11] although no bands in the infrared spectra were sufficiently distinct to be unequivocally assigned to this system.[12] The resistance to hydrogenation of XV further suggests that the ethylenic system is not disubstituted, and the friedelane skeleton does not permit the existence of a tetrasubstituted double bond. In addition, the nuclear magnetic resonance spectrum[13] of the ketone (XIII) run in deuterochloroform solution with tetramethylsilane as an internal reference at 60 mc frequency showed a singlet signal at 300 cps attributable to an olefinic proton not conjugated with the carbonyl group.

The location of the double bond introduced by the action of N-bromosuccinimide on bromoketones (II) and (III) and hydrocarbon (XVI) is consequently restricted to position 1(10), 7 or 18. The exclusion of positions 1(10) and 7 was effected by examining the dehydrobromination of XII with silver acetate in the manner previously employed for the transformation III → IX + X. Under these conditions, there was isolated a dehydrobrominated product, $C_{30}H_{46}O$, which showed no high intensity ultraviolet absorption above 220 mμ. Since there is no conjugation of carbonyl or ethylenic functions in this dienone product, the original double bond could not have been located in ring A or B.

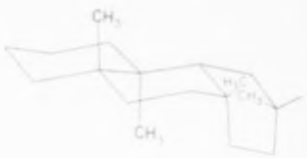
Although there has been much work on synthetic applications of allylic bromination

[10a] L. Ruzicka, H. W. Huyser, M. Pfeiffer and C. F. Seidel, *Liebigs Ann.* **471**, 21 (1929).
[b] L. Ruzicka, H. Silbermann and M. Furter, *Helv. Chim. Acta* **15**, 482 (1932).
[11a] T. G. Halsall, *Chem. & Ind.* 867 (1951).
[b] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).
[12] A. R. H. Cole and D. W. Thornton, *J. Chem. Soc.* 1332 (1957) have noted very low C=C stretching intensity in Δ^{18}-unsaturated pentacyclic triterpenoids.
[13] We are indebted to Dr. Leroy Johnson (Varian Associates) for this determination.

and detailed mechanisms have been forwarded,[14] comparatively little is known with regard to the action of N-bromosuccinimide on saturated systems. It has been established that cyclohexane[15,16] and cycloheptane[16] yield the cycloalkyl bromide with N-bromosuccinimide under certain conditions and that decalin gives a tetrabromo-octahydronaphthalene[17] which can also be obtained from the probable intermediate 9,10-octalin. Cason and coworkers[18] have also drawn attention to the fact that N-bromosuccinimide is not a reagent of general utility for the α-bromination of saturated esters due to selective attack on tertiary hydrogen atoms at other sites in the molecule.



XVII



XVIII

The experiments described in this work establish that in friedelin, the tertiary axial α-hydrogen atom at position 4 is more reactive towards N-bromosuccinimide than the secondary hydrogen atoms at position 2, but that the presence of a 2α-bromine atom effectively prevents abstraction of the 4α-hydrogen atom by its 1:3-diaxial blocking effect to the approach of a succinimide radical. In absence of the activating C-3 carbonyl group or where there is deactivation due to the steric influence of the neighboring axial halogen, the most reactive hydrogen is the tertiary C-18 atom. An examination of an all-chair form (XVII) of friedelane shows that, as a consequence of the *cis*-junction of rings D and E, a severe steric interaction must exist between the 13α- and 20α-methyl groups. Whereas this interference is removed if the terminal ring E adopts a boat conformation (XVIII),[19] an unfavorable 1:4-diaxial "boat prow-and-stern" methyl interaction is a consequence. The steric strain inherent in both conformations of this *cis* D/E system is relieved by dissociation of the 18β-hydrogen atom and formation of the ethylenic trigonal system. The driving force for the backbone rearrangement[20] of friedelene (VI) to the oleanenes (VII) and (VIII) can be attributed also to the same steric interactions.

EXPERIMENTAL[21]

4α-Bromofriedelin (III). N-Bromosuccinimide (150 mg) was added to a solution of friedelin (250 mg) in carbon tetrachloride (70 cm³) and the mixture heated under reflux by means of infrared lamp. After about 12 min an orange color appeared, followed by decolorization over 30 sec. After a

[14] H. J. Dauben, Jr. and L. L. McCoy, *J. Amer. Chem. Soc.* **81**, 4863 (1959) survey reaction variables in terms of mechanism and give leading references to previous work.
[15] M. C. Ford and W. A. Waters, *J. Chem. Soc.* 2240 (1952).
[16] Ng. Ph. Buu-Hoï and P. Demerseman, *J. Org. Chem.* **18**, 649 (1953).
[17] R. A. Barnes, *J. Amer. Chem. Soc.* **70**, 145 (1948).
[18] J. Cason, N. L. Allinger and D. E. Williams, *J. Org. Chem.* **18**, 842 (1953).
[19] C. Djerassi, J. Osiecki and W. Closson, *J. Amer. Chem. Soc.* **81**, 4587 (1959).
[20] W. Laird, F. S. Spring and R. Stevenson, *J. Amer. Chem. Soc.* **82**, 4108 (1960).
[21] All melting points were determined on a Gallenkamp melting point apparatus. Unless otherwise noted, rotations were measured in chloroform solution. The microanalyses were determined by Schwarzkopf Microanalytical Laboratory (Woodside, N.Y.).

reaction time of 30 min, the mixture was cooled, filtered and the solvent removed. The residue was recrystallized twice from chloroform–methanol to give 4α-bromofriedelin as needles (110 mg), m.p. 198–199°, $[\alpha]_D$ +92° (*c*, 1·3), $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 308·5 mμ. Lit.[2] m.p. 196–197°, $[\alpha]_D$ +90·5°.

2α-*Bromofriedelin* (II). (a) A saturated solution (2 drops) of hydrogen bromide in chloroform was added to a solution of friedelin (1·53 g) in chloroform (50 cm³), followed by a solution of bromine (0·658 g) in chloroform (15 cm³). The bromine color faded almost immediately to pale yellow which persisted after stirring for 15 min, when the solvents were removed under reduced pressure. Crystallization of the residue from chloroform–methanol gave needles, m.p. 206–207°, $[\alpha]_D$ −117° which after two further recrystallizations gave 2α-bromofriedelin (751 mg), as colorless needles, m.p. 214° (dec.), $[\alpha]_D$ −140° (*c*, 1·1), $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 310 mμ. Lit.[3] m.p. 210°, $[\alpha]_D$ −140°.

(b) A solution of bromine (34 mg) in acetic acid (10 cm³) was added dropwise over 20 min to a solution of 4α-bromofriedelin (100 mg) in ether (30 cm³) and acetic acid (50 cm³). The residue, after removal of solvents under reduced pressure, was crystallized twice from chloroform–methanol to give the 2α-bromoketone (25 mg), m.p. and mixed m.p. 216–216·5°, $[\alpha]_D$ −140°, $\lambda_{max}^{CHCl_3}$ 310 mμ.

Attempted bromination of the 4α-bromoketone in carbon tetrachloride solution in the absence or presence of calcium carbonate yielded only unchanged starting material. The specific rotation of the 4α-bromoketone in chloroform solution containing hydrogen bromide changed on standing from +90° to +8° (5 min), ±0° (1 hr), −11° (2 hr), −71° (14 hr) and −78° (24 hr). The specific rotation of 2α-bromoketone in chloroform saturated with hydrogen chloride changed to −74° after 24 hr.

2α-*Bromofriedel*-18-*en*-3-*one* (XI). N-Bromosuccinimide (43 mg) was added to a solution of 2α-bromofriedelin (100 mg) in carbon tetrachloride (70 cm³), the mixture refluxed for 30 min with an infrared lamp and worked up in the usual way. Crystallization of the product from chloroform–methanol gave 2α-*bromofriedel*-18-*en*-3-*one* as small needles (32 mg), m.p. 207–208° (dec.), $[\alpha]_D$ −139° (*c*, 2·0), $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 311 mμ. Ultraviolet end absorption, *ε* 750 (220 mμ), 1990 (215 mμ), 4350 (210 mμ), $\lambda_{max}^{CS_2}$ 3·45, 3·50, 5·84, 7·22, 7·40, 8·25, 8·45, 8·49, 8·93, 9·83, 10·00, 10·20, 10·92, 11·64 μ. It gives a yellow color with tetranitromethane in chloroform solution.

(Found: C, 71·42; H, 9·48; Br, 16·35. Calc. for $C_{30}H_{47}OBr$: C, 71·55; H, 9·41; Br, 15·87%).
R.D. in dioxane (*c*, 0·053): $[\alpha]_{700}$ −34°, $[\alpha]_{589}$ −117°, $[\alpha]_{365}$ −3370°, $[\alpha]_{330}$ +3717°, $[\alpha]_{280}$ +2620°.

Friedel-18-*en*-3-*one* (XIII). Zinc dust (13 g) was added portionwise over 1 hr to a refluxing solution of 2α-bromofriedel-18-en-3-one (365 mg) in benzene–ethanol (1:1, 150 cm³). After a further reflux period of 2 hr, the hot solution was filtered and the solvents removed under reduced pressure. The residue was extracted with chloroform, the extract washed with water, dried (Na_2SO_4) and evaporated to give the product which was crystallized from chloroform–methanol to give *friedel*-18-*en*-3-*one* as needles, m.p. 266–269°, vac. m.p. 280–282°, $[\alpha]_D$ −28° (*c*, 2·05) $\nu_{max}^{CHCl_3}$ 1706 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 290 mμ (inflexion), $\lambda_{max}^{CS_2}$ 3·45, 3·50, 5·85, 7·22, 7·27, 7·40, 8·22, 8·37, 9·05, 9·33, 9·83, 10·93, 11·65 μ. It gives a yellow color with tetranitromethane in chloroform solution.

(Found: C, 84·58; H, 11·19. Calc. for $C_{30}H_{48}O$: C, 84·84; H, 11·39%).
R.D. in dioxane (*c*, 0·052): $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ ±0°, $[\alpha]_{314}$ −1610°, $[\alpha]_{275}$ +1490°, $[\alpha]_{250}$ −954°.

Friedel-18-*en*-3β-*ol* (XIV, R = H). A solution of friedel-18-en-3-one (300 mg) in anhydrous ether (150 cm³) was refluxed with lithium aluminum hydride (250 mg), the product isolated in the usual way and crystallized from chloroform–methanol to give needles, m.p. 273–275°. Recrystallization from chloroform–ethyl acetate yielded *friedel*-18-*en*-3β-*ol* as needles, m.p. 277–279°, $[\alpha]_D$ +25° (*c*, 1·2). Ultraviolet end absorption, *ε* 590 (220 mμ), 1420 (215 mμ), 3520 (210 mμ). $\lambda_{max}^{CHCl_3}$ 3·45, 3·50, 6·86, 7·26, 7·36, 9·85, 10·10, 10·34, 10·90, 11·64 μ. It gives a yellow color with tetranitromethane in chloroform.

(Found: C, 83·88; H, 11·72. Calc. for $C_{30}H_{50}O$: C, 84·44; H, 11·81%).

Friedel-18-*en*-3β-*yl acetate* (XIV, R = Ac). Treatment of the alcohol (50 mg) with acetic anhydride (2 cm³) in pyridine (1 cm³) at 100° for 1 hr and working up in the usual way gave a solid, which was crystallized from chloroform–methanol to give *friedel*-18-*en*-3β-*yl acetate* as needles (32 mg), m.p. 281–282°, $[\alpha]_D$ +30° (*c*, 1·34). $\lambda_{max}^{CS_2}$ 3·44, 3·50, 5·77, 7·22, 7·30, 7·38, 8·07, 8·22, 8·60, 9·85, 10·26, 11·66 μ. It gives a yellow color with tetranitromethane in chloroform.

(Found: C, 81·99; H, 11·18. Calc. for $C_{32}H_{52}O_2$: C, 82·63; H, 11·38%).

Friedel-18-*ene* (XV). Potassium hydroxide (1·7 g) and hydrazine hydrate (99–100%, 2 cm³) were added to a suspension of friedel-18-en-3-one (170 mg) in diethylene glycol (17 cm³), the mixture refluxed for 1 hr, the temperature raised to 210° by concentration of the solution, and refluxing continued for a further 5 hr. After cooling the mixture was poured into water (50 cm³), extracted with

chloroform (3 × 50 cm³), and the extract washed with water and dried (Na_2SO_4). Removal of the solvent gave a solid (80 mg) which after several recrystallizations from chloroform–methanol or chloroform–ethyl acetate gave *friedel*-18-*ene* as needles, m.p. 242–244°, $[\alpha]_D$ +17° (*c*, 1·6), $\lambda_{max}^{CS_2}$ 3·45, 3·50, 7·22, 7·27, 7·43, 8·35, 9·19, 9·32, 9·52, 9·82, 10·05, 10·22, 10·90, 11·63, 14·20 μ. Ultraviolet end absorption, ε 670 (220 mμ), 2140 (215 mμ), 4080 (210 mμ). It gives a yellow color with tetranitromethane in chloroform.

(Found: C, 87·97; H, 11·99. Calc. for $C_{30}H_{50}$: C, 87·73; H, 12·27%).

The hydrocarbon was recovered unchanged from attempted hydrogenation with platinum oxide in cyclohexane–acetic acid at atmospheric and 39 lbs/in² pressure and from treatment with osmium tetroxide in ether–pyridine solution.

18ξ:19ξ-*Epoxyfriedelane*. A chloroform solution (5 cm³) of perbenzoic acid (62 mg/cm³) was added to friedel-18-ene (96 mg) in chloroform (20 cm³) and allowed to stand at 5° for 24 hr. (Estimated uptake was 0·93 mole.) After washing with potassium bicarbonate solution and water, the dried (Na_2SO_4) solution was evaporated to give a solid, m.p. 238–239°, $[\alpha]_D$ +35° (*c*, 1·6). Five more recrystallizations from chloroform–ethyl acetate gave 18ξ:19ξ-*epoxyfriedelane* as needles, m.p. 260–261°, $[\alpha]_D$ +34° (*c*, 1·2). It gives no color with tetranitromethane and shows no carbonyl absorption in the infrared. $\lambda_{max}^{CHCl_3}$ 3·46, 6·84, 7·24, 7·35, 9·00, 10·05, 10·65, 10·95, 11·93 μ.

(Found: C, 84·28; H, 11·93. Calc. for $C_{30}H_{50}O$: C, 84·44; H, 11·81%).

4α-*Bromofriedel*-18-*en*-3-*one* (XII). (a) N-Bromosuccinimide (32 mg) was added to a solution of friedel-18-en-3-one (70 mg) in carbon tetrachloride (20 cm³), the mixture refluxed with irradiation from an infrared lamp for 30 min, cooled and filtered. The residue, obtained on evaporation of the filtrate was crystallized from chloroform–ethyl acetate to give the product (35 mg, m.p. 180–181°) which on two further recrystallizations from the same solvents yielded 4α-*bromofriedel*-18-*en*-3-*one* as very fine needles, m.p. 185–186°, $[\alpha]_D$ +87° (*c*, 1·62), $\lambda_{max}^{CHCl_3}$ 307 mμ, $\lambda_{max}^{CHCl_3}$ 3·45, 3·50, 5·86, 6·24 (*w*), 6·88, 7·21, 7·26 (*sh*), 7·36, 7·60, 9·06, 9·17, 9·31, 9·83, 10·19, 10·45, 10·95, 11·62 μ. It gives a yellow color with tetranitromethane in chloroform solution.

(Found: C, 71·80; H, 9·83. Calc. for $C_{30}H_{47}OBr$: C, 71·55; H, 9·41%).

R.D. in dioxane (*c*, 0·050): $[\alpha]_{700}$ +104°, $[\alpha]_{589}$ +80°, $[\alpha]_{334}$ +1450°, $[\alpha]_{285}$ −1904°, $[\alpha]_{265}$ −1564°.

(b) N-Bromosuccinimide (75 mg) was added to a solution of 4α-bromofriedelin (200 mg) in carbon tetrachloride (53 cm³). Treatment as in (a) above gave the crude unsaturated bromoketone (115 mg, m.p. 178–181°) which on two further crystallizations yielded 50 mg, m.p. 186–187°, $[\alpha]_D$ +86° (*c*, 2·56) with identical infrared spectrum. In another experiment, 1·2 g of 4α-bromofriedelin gave 0·6 g of pure 4α-bromofriedel-18-en-3-one.

Debromination of 4α-bromofriedel-18-en-3-one (300 mg) by zinc in benzene–alcohol as described for the 2α-bromo isomer gave friedel-18-en-3-one (148 mg) as needles, m.p. and mixed m.p. 266–269°, $[\alpha]_D$ −26° (*c*, 1·85).

The action of silver acetate on 4α-*bromofriedel*-18-*en*-3-*one*. A solution of 4α-bromofriedel-18-en-3-one (115 mg) in ether (50 cm³) was added to a solution of silver acetate (112 mg) in water (2 cm³) and acetic acid(60 c m³). The mixture was distilled until the boiling vapor temperature was 110°, refluxed for 20 min filtered and evaporated. The residue was extracted with chloroform (150 cm³), the extract washed with water, dried (sodium sulfate) and the product, obtained on evaporation, was crystallized from chloroform–methanol to give a product (48 mg) regarded as a mixed crystal (needles) of *alnusa*-5:18-*dien*-3-*one* and *alnusa*-5(10):18-*dien*-3-*one*, m.p. 233–235°, $[\alpha]_D$ −42·5° (*c*, 1·46). It gives a yellow color with tetranitromethane in chloroform solution and shows no high-intensity ultraviolet absorption. Ultraviolet end absorption: ε 1055 (220 mμ), 2020 (215 mμ), 4960 (210 mμ).

(Found: C, 85·01; H, 10·98. Calc. for $C_{30}H_{46}O$: C, 85·24; H, 10·97%).

2α-Bromofriedel-18-en-3-one was recovered unchanged after identical treatment.

Action of N-*bromosuccinimide on friedelane*. N-Bromosuccinimide (98 mg) was added to a solution of friedelane (200 mg, m.p. 252–254°, $[\alpha]_D$ +21°, prepared by Huang-Minlon reduction of friedelin) in carbon tetrachloride (100 cm³), and the mixture heated by an infrared lamp. A yellow color appeared after refluxing for 12 min, then disappeared after a further 30 sec. After a total reflux time of 30 min, the mixture was cooled, filtered and the solvent removed under reduced pressure. Crystallization of the solid residue from chloroform–ethyl acetate gave a product, m.p. 220–221°, unchanged on two further crystallizations. Two further crystallizations from a larger volume of these solvents gave friedel-18-ene as blades, m.p. and mixed m.p. 242–245°, $[\alpha]_D$ +17° (*c*, 1·6). The infrared spectrum (in KBr pellet) was superimposable on that of the sample obtained by Huang-Minlon reduction of

friedel-18-en-3-one and had bands at 1650 (weak), 1465, 1440, 1385, 1360, 1318, 1265, 1160, 1123, 1092, 1079, 1054, 1020, 1000, 981, 964, 948, 920, 821, 680 cm^{-1}.

In another similar experiment, friedelane (300 mg) yielded friedel-18-ene (75 mg, m.p. 241–242°), raised to m.p. 242–244°, $[\alpha]_D$ +18·5° (*c*, 1·52) after a further crystallization.

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Tetrahedron, 1961, Vol. 15, p. 231. Pergamon Press Ltd. Printed in Northern Ireland

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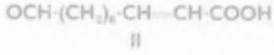
ERRATUM

R. H. JAEGER and Sir ROBERT ROBINSON: A simple synthesis of "Queen substance", *Tetrahedron* **14**, 320 (1961).

Formula II, on p. 320 of the above, should read as follows:



II

Tetrahedron, 1961, Vol. 15, p. 232. Pergamon Press Ltd. Printed in Northern Ireland

A list of papers to be published in a future issue

An Epistologue on the Effect of Environment on the Properties of Carbon Bonds*

D. R. LIDE, JR.: A survey of carbon–carbon bond lengths.

B. P. STOICHEFF: The variation of carbon–carbon bond lengths with environment as determined by spectroscopic studies of simple polyatomic molecules.

O. BASTIANSEN and M. TRAETTEBERG: The nature of bonds between carbon atoms. How they vary with environment.

D. W. J. CRUICKSHANK: X-ray results on aromatic hydrocarbons.

D. J. MARAIS, N. SHEPPARD and B. P. STOICHEFF: An investigation of the structure of butadiene by high resolution infra-red and Raman spectroscopy.

L. OLEARI: Electronic wave function of methane and C—H bond orbital.

L. S. BARTELL: On inferences of bond character from bond length: the important rôle of non-bonded interactions.

E. BRIGHT WILSON, JR.: Conjugation, hybridization and steric hindrance in relation to bond lengths.

W. M. SCHUBERT, R. B. MURPHY and J. ROBINS: Electron donor and acceptor properties of alkyl substituents.

C. A. COULSON and W. T. DIXON: Bond lengths in cyclic polyenes C_nH_n—a re-examination from the valence-bond point of view.

LINUS PAULING: The carbon–carbon triple bond and the nitrogen–nitrogen triple bond.

I. FISCHER-HJALMARS: On the nature of bonds between carbon atoms.

M. I. KABACHNIK, T. A. MASTRYUKOVA and T. A. MELENT'YEVA: Conjugation in systems with a tetrahedral atom. Diarylphosphonic acids.

R. DAUDEL: Remarks concerning the effect of environment on the properties of Cl and CO bonds.

* No. 3 in the Contributed Symposia on Recent Developments in Organic Chemistry.

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